HOUSE OF COMMONS SESSION 1994–95

SCIENCE AND TECHNOLOGY COMMITTEE

HUMAN GENETICS

VOL. II

Memoranda received up to January 31st 1995

Ordered by The House of Commons *to be printed*
18 January 1995

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LIST OF MEMORANDA

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Press release issued by the Committee (3 November 1994)

HUMAN GENETICS

The Science and Technology Committee's next major inquiry will be into the ethical, regulatory and economic implications of human genetic research. It will examine the current state and future potential of the science of human genetics. The Committee will address the key ethical and social concerns which surround this area of scientific endeavour, and the regulatory structures which guide and constrain it now, and those which will be needed in the future, at the national and international levels. As part of this inquiry the Committee will also examine the Human Genome Mapping Project to see how this vast international project is organised and financed, and what it may achieve.

The Committee feels the inquiry is timely, since both the Council of Europe and UNESCO are currently studying the issue. It is expected that there will be a declaration on the protection on the human genome in 1998, possibly followed by an international treaty. The Committee trusts its inquiry will help to inform such international decision making.

The key questions the Committee will be considering are:

- What is the current state of the science; what are its current directions of development, the factors influencing development and the likely time scale of development of the science and its applications?
- What are the driving forces behind the science?
- Are there only benefits or will some people suffer as a consequence of this research?
- What are the social, ethical and medical implications of this research?
- How are genetic research and its applications financed and managed, how much is spent on them and by whom, and is the level of investment appropriate to the potential outcome of such genetic research?
- How should the research be regulated?

Among others, the Committee will seek evidence from the MRC, other funders of research, medical organisations, patients' organisations, pharmaceutical companies, insurers and individual researchers. A full list of the general questions posed to the various witnesses is attached.

Those wishing to submit a memorandum on any or all of the areas under consideration are asked to send it to the Clerk of the Science and Technology Committee, House of Commons.

HUMAN GENETICS: QUESTIONS

The Committee wish to focus their inquiry on the ethical, regulatory, social and economic issues raised by human genetics research. The principal issues are set out below.

1. GENERAL ETHICAL AND REGULATORY

1.1 What do we need to know about the way genes work in order to make decisions about the use or regulation of genetic information? Are we likely to obtain that information?

1.2 Are the current policies being pursued by the MRC and other research funding bodies with regard to ethical and social consequences of research in human genetics adequate?

1.3 Has society a right to declare that some research topics should be prohibited because they are intrinsically likely to lead to insuperable moral problems? Should geneticists think more widely than their immediate research goals and their likely consequences or should they leave that to others? Are they pursuing hidden agendas of which the public is unaware?

1.4 Does research into human genetics lead to a deterministic or any other particular view of human behaviour? Will people try to improve the world through genetic interventions? Should they?

1.5 Germ line intervention would affect later generations who cannot give their assent. Are there other objections in principle to it which go beyond our limited knowledge of what those effects might be? Would this be playing God? What does that mean and why would it be wrong?

1.6 What should the proposed UN declaration and treaty on the protection of the human genome say?

2. PUBLIC AWARENESS AND EDUCATION

2.1 What is the extent of knowledge of and interest in genetics among different sectors of the public. Should steps be made to improve this and, if so, what form should they take?

2.2 Is there a general anxiety and suspicion about research in genetics? It is justified or should it be allayed and, if so, how?

2.3 Are there unreasonable expectations of the benefits that might come from genetics? If so, should these be tempered?

2.4 Is there a danger that genetics will be seen as an excuse for socially unacceptable behaviour? Could it be used to justify reductions in social programmes of health, education and welfare?

2.5 What are the right questions on the bearing of genetics on human behaviour, ethics and belief?

3. GENETIC DISEASE

3.1 How much of genetic diagnosis is conducted as a routine medical service and how much is associated with research programmes? Is the continuity between the two sufficiently well organised? Are some diseases with a known genetic cause not being diagnosed and, if so, why not?

3.2 Are there any ethical questions about somatic cell gene therapy which are different from other types of therapy which affect only the patient receiving them?

3.3 Should information about an individual's genome be regarded as confidential or should it be possible for employers, insurance companies etc., to require genetic tests or to obtain the results of previous tests on an individual or their relatives? If not, why is genetic testing any different from current medical tests?

3.4 When is population screening for genetic disease appropriate? What factors, such as cost and the availability of counselling and treatment, should be taken into account? How should screening be organised and regulated?

3.5 If screening for a wide range of genetic predispositions becomes routine, how will people be protected from discrimination on the grounds of their genotype? Should they be?

3.6 Would people be well advised to seek genetic information from sexual partners before the conception of children? Are they likely to? Is this likely to change with future research?

4. ECONOMIC BENEFITS

4.1 What assistance in the treatment of disease or the design of drugs is given by knowledge of the gene(s) associated with a particular disease?

4.2 Are there differences, in principle or in practice, between gene and conventional therapy? How might these affect development costs? How will this affect the actual cost of treatment?

4.3 To what extent do factors, such as technology-transfer facilities, patent protection and regulation, influence the commercial exploitation of research findings?

4.4 How does the regulatory regime for genetic-based industry in the UK compare with that in other countries? Is there a danger that investment will be lost to other countries with different regulations or with better venture capital funding potential?

4.5 What products, other than medical diagnostics and therapies, might be produced as a result of human genetic research?

In reaching conclusions on the above matters it is necessary to consider the scientific background. The following questions aim to address this.

5. RESEARCH

5.1 Why is it worthwhile to map and sequence the human genome? What are the relative advantages of mapping expressed genes only versus completely sequencing the genome?

5.2 What will it tell us about the human species and the individual that would not otherwise accrue from piecemeal studies?

5.3 To what extent are human characteristics determined by the genome and to what extent does the environment influence the expression of genes?

5.4 How much is understood about the organisation of coding information in the genome? Is it conceivable that interventions such as those produced by gene therapy might have unforeseen effects?

5.5 Is the financial support for research in human genetics adequate when compared with the results which may flow from it?

6. Evolution

Some public concerns reflect unease about the possible effect of genetic interventions on the long-term future of the human race:

6.1 What evidence is there of continuing evolutionary change in humans?

6.2 What may be the consequences of modern social organisation for human evolution?

6.3 What may the consequences of environmental change be for human evolution?

6.4 What may be the consequences of the pursuit of scientific knowledge for human evolution?

6.5 What might be the evolutionary impact of selective fertilisation or termination and of other forms of extreme discrimination?

6.6 In what ways does manipulation of the germ line in the clinic or laboratory differ from natural variation?

6.7 Human evolution has been by sexual reproduction guided by human behavioural drives. Should clinical interventions be allowed to interfere with this process?

Memorandum from Sir Cecil Clothier (HGB1) (July 1994)

The Committee will be aware from its wide experience that there has been no human invention so benign but that someone has found a way to abuse it, usually for gain.

The mapping of the entire human genome, a project the achievement of which is now in sight, will offer great potential for the relief of suffering, but at the same time will offer many opportunities for misuse.

Anxiety about possible abuse of genetic information relating to individuals has been expressed in many reports and writings. See, for example, the Report of the Nuffield Council on Bioethics entitled "Genetic Screening Ethical Issues" and the Report of the Departmental Committee on the Ethics of Gene Therapy (Cm 1788) which contains also a bibliography of writings on ethical problems arising from the ability to alter or repair defective genes. It contains also a simplified account of genes and their functions. The ability to modify or replace defective genes is rapidly approaching and is intricately involved with the Human Genome Project. It is obvious enough that the greater our knowledge of an individual's genetic make-up, the greater the possibility of relieving illness and disability by means of gene therapy. Whatever regulating mechanism may ultimately be thought desirable for the use of genetic information, it should be such as to promote the proper uses of gene therapy.

This technology may lead us to the prevention or cure of genetically mediated diseases, many of which are incurable at present and treatable only in a very limited way. They cause great suffering and disability to the patients and inflict a great burden and much sorrow on their families. Well known examples are Duchenne Muscular Dystrophy, Cystic Fibrosis and Huntington's Chorea. All of these are fatal, but only after a long course of increasing suffering for all concerned.

At present there is almost universal acceptance in the developed countries that the use of gene therapy to prevent or repair defective genes in an individual should be confined to treating the somatic cells of the person, i.e., those body cells, the genes of which never pass to descendants. Germ line cells are those in the gonads which humans can pass to subsequent generations. As yet no civilised country has proposed to modify or treat these cells because of the implications for the future about which we do not yet know enough.

Yet here there will arise eventually an ethical and philosophical problem of just the kind the regulation of which the Committee is probably contemplating. At present we await the event of birth and early development and when a disease process becomes evident we endeavour to treat it. But with the advent of much greater knowledge of the human genome, it will be possible to detect and perhaps repair genetic defects in utero, thus obviating must of the suffering. Logic then poses the question: "Why do you wait until a defective embryo is formed in some unfortunate woman's uterus and then declare that you will undertake to treat it?" With the greater knowledge which we may soon have, a genetic defect in a person's germ cells may be detected and either repaired or treated before an embryo is conceived. The objection that the altered genes may be passed to subsequent generations may in the light of greater knowledge seem to be a benefit rather than a danger. But that way lies the socalled "eugenics" about which most people rightly feel deep anxieties and suspicion. I propose

no solution to this problem, but invite the Committee to the view that some sort of national regulatory body, competent to consider such problems and to speak for our country internationally, must soon be created.

Specific problems

However, there are more immediate problems for such a body to consider, arising from the completion of the Human Genome Project. Some of the main topics of anxiety have been identified:

1. *Information*

The public, it is said, does not yet know enough about genetics to perceive the ethical problems which may arise, or to make intelligent decisions on their own behalf about genetic information concerning themselves which may soon become available. It is not easy to see this as a matter for regulation. There is a vast literature already in existence, ranging from child's guides to advanced technical studies on the subject of genetics. The public cannot be made to inform itself if it will not trouble to do so, as all government departments discovered long ago. However, there is room for providing that the implications and possible consequences of genetic screening for whole families should be made known to those being treated or merely diagnosed as having genetic defects. This is the process nowadays known as "counselling". Previously it was regarded merely as good communication between doctors and their patients and families.

2. *Confidentiality*

There is an obvious field for close control in the uses to which genetic information resulting from screening or testing is put. First and foremost there will be a need to reconsider the ancient doctrine of medical confidentiality. This doctrine already has distinct limitations, as any doctor knows who has had as a patient an airline pilot complaining of dizzy spells or other condition relevant to that occupation. Those who may in future practise genetic screening or gene therapy may need to be subject to clear regulation as to the uses which may be made of information obtained about patients or other needing or asking to know about their genetic makeup; for example, prior to marriage. Others beside the patient or enquirer might need to be informed of matters closely affecting their health or well being. It may not be enough to try to persuade patients or others by counselling that they have a moral obligation to consent to the release of information about themselves. It may require some sort of legal duty. Registers may need to be kept of persons known to suffer from a serious genetic defect leading to terrible diseases such as Huntington's Chorea.

3. *Life assurance*

Many life insurers and providers of pensions and accident insurance will have an obvious interest in the genetic makeup of proposers for cover, which may profoundly affect their insurability. Some proposers for life assurance may find that they are virtually uninsurable because their genetic makeup predicts an early death. For example, there is evidence already that one of the commonest causes of premature death in males, coronary artery disease, has a genetic origin. The disease is detectable in the arteries of children at autopsy, which strongly suggests that hereditary causes rather than lifestyle are at work. And there is yet stronger evidence of a familial proneness to some type of cancer. No doubt other examples of genetically transmitted disease, or proneness thereto, will be discovered.

A philosophical problem here is that all insurance contracts are in essence a respectable form of gambling transaction in which the insurer calculates the odds on the insured event happening or not, or happening earlier or later, and adjusts the premium accordingly. If the insured fails to disclose in advance some highly relevant fact suggesting that the outcome is certain, that party resembles the gambler who places a bet on a horse race at a time when he knows what the result is going to be. Hence the clause in contracts of insurance requiring the proposer to disclose all relevant facts, otherwise the contract will be void.

At present, insurers are not asking for genetic information about their clients, but one wonders how long this will remain their policy. Some day it may be difficult or impossible for some people to obtain motor insurance on the mere suspicion of a liability to heart failure or other suddenly disabling condition.

4. *Employment*

The interest of employers in the future in the genetic inheritance of potential employees is obvious. Knowledge of genetic makeup may save some possible employees from a highly unsuitable working environment. But the same knowledge might also give rise to an unfair discrimination against individuals who are in every other way fit and proper employees.

5. *Police*

The possibility of eliminating whole populations of an area from suspicion of a particular crime by reference to their registered genetic makeup is obviously an attractive one for the police. At its meeting this autumn, the

British Association for the Advancement of Science was told that it may soon be possible to reconstruct facial features from traces of blood or semen left at the scene of a crime. But there is the unattractive possibility of suspicion falling on innocent persons simply because of their supposed hereditary tendency to commit certain kinds of crime, or even because of some facial resemblance constructed from genetic information.

Regulation

We are all familiar with close regulation of a great range of human activity, never more so than with the advent of the European Union. Whatever view one may take of some regulatory fields, few could doubt that the user of genetic information should be subject to some form of control.

The danger of overmuch regulation is that it may stifle initiative and progress in some field where the people should have the benefit of some scientific advance, sooner rather than later, for example from a new and potent drug. Criticism of the Food and Drug Administration in the United States has often focused on the inhibitory and delaying consequences of its elaborate regulations, which have been known to prevent medicines being available there, the benefits of which were being enjoyed elsewhere.

As in so much of government, balance is everything. Overmuch regulation stultifies inventiveness: too little facilitates abuse.

Fortunately we have a good recent example of regulation in the medical field. When in vitro fertilisation (IVF) was first developed and doctors began to offer treatment to patients on a countrywide basis, it was soon apparent that certain standards of medical and laboratory competence, record keeping, hygienic storage, confidentiality and so forth, needed to be established. Those concerned in the work, with the help of the Royal College of Obstetricians and Gynaecologists, set up a body called the Voluntary Licensing Authority (VLA) to define the necessary standards. The Authority also visited and inspected hospital and other premises where the work was carried on and granted licences to practise the technique. This body had only the authority of its prestige. But since practitioners at that time were few and of undoubted integrity, they accepted this form of voluntary control of their work.

After about five years, the technique became more widely known. It began to be offered in many locations by persons not hitherto practising it, some of whom used methods which the VLA had disapproved, from premises which were unsuitable and with inadequate laboratory facilities. Once the nature and form which common abuses of the technique took became clear, the way was open for legal regulation. After some pressure, the government enacted the Human Fertilisation and Embryology Act 1990 which established a statutory body with powers to license IVF Centres and imposed sanctions for failure to observe the provisions of the Act.

The advantage of proceeding in these two stages is now established. At first, a new technique is in the hands of a few very expert and honourable persons, in well equipped centres, who can be trusted to follow only the best methodology and who join together to set up ethical standards. The new discovery develops fast without hindrance but under competent and wise control.

After a time the new technique becomes easier to master and is more widely practised, whereupon certain abuses begin to emerge. The persons responsible are usually those who are unwilling to accept voluntary control which often stands in the way of profit. Then when these abuses are identified, it is possible to formulate rules with the force of law to regulate the practice of the technique and to license only fit and proper persons to exercise it.

The creation of a regulatory body, usually with the title of "Authority", is now a familiar part of our administrative law. In the present context, one would expect its composition to embrace persons of known integrity and experience in the field to be controlled and an equal or slightly larger number of people who can represent the nonscientific general public. I am quite disinterested in saying that at least one person qualified in the practice of the law should be included. This is necessary to ensure both that the Authority exercise its powers fully and on the other hand that it does not exceed them. It is also important that the Authority should not be intimidated by empty threats of legal proceedings.

Above all, I suggest to the Committee that the Authority should be kept small, to perhaps a dozen members. Large bodies of this nature tend to take a very long time to arrive at conclusions which are the lowest common factor of agreement in their deliberations. It has been said that the French National Ethical Council suffers from the defect of being so large as to be practically impotent.

It is not necessary or desirable in my experience to try to represent in the membership all relevant currents of public opinion. Discriminating between contestants for a seat on the Authority leads to friction and ill feeling. And members put forward by a particular constituency of opinion find themselves campaigning instead of debating with an open mind, which is what they were appointed to do.

Finally, I draw attention to an intractable problem which a regulatory body might need to consider. At present, for the most part, the right to personal integrity stands firm. One does not need to give a blood sample unless

one is willing; to take one by force is in general an unlawful trespass to the person. Having voluntarily given a blood sample, however, one must be deemed to have consented to all the information it yields being recorded in one's notes and available to those with a legitimate interest in studying them. This generally maintains the confidentiality of the information.

Such, however, is the power of the coming technology of genetic analysis, that the smallest accidental excretion of bodily fluids, saliva for example, will yield the whole of one's genetic construction to anyone who troubles to salvage and analyse it. This opens wide the way to misuse of genetic information.

Letter from Dr D Geddes, Consultant Physician The Royal Brompton Hospital (HGC2) (8 November 1994)

Thank you for your letter and the enclosed press release. I would like to make two statements in relation to the development of somatic gene therapy for inherited diseases.

1. There is an increasing consensus that there are no important new medical, ethical or safety issues involved in the development of somatic gene therapy as compared with the development of chemical therapies. This was concluded by the Clothier Committee and is in line with previous deliberations of the Warnock Committee. There may have been some public concern about this aspect of gene therapy at first, but this has been increasingly allayed by the very widespread publicity and responsible debate that has taken place over the last three years. In spite of this, the approach to regulation of human somatic gene therapy research for inherited diseases has been somewhat restrictive and inflexible. The Gene Therapy Advisory Committee chaired by Dame June Lloyd has played a valuable part in furthering the debate and goes to great trouble first to ensure correct ethical standards, but secondly to avoid imposing unnecessary delay and constraints on research which might benefit people who are suffering from and often dying from inherited diseases. The same enlightened approach not been adopted by the Medicines Control Agency. This Agency seems to have been surprisingly slow and reticent in taking part in the debate and in formulating its own rules of conduct for assessing research of this sort. At present gene therapy research is subjected to more regulations than any other form of new treatment at the very earliest stage and rules that were formulated to control the commercial development of new chemical drugs to be taken by large numbers of people are being applied in a restrictive way to very early human experiments in gene therapy. This is in marked contrast to the much more co-operative and helpful attitude taken by the Federal Drugs Administration Committees in the United States. The FDA attends research meetings and takes part in useful dialogue with medical research workers to ensure high standards, but also to facilitate rather than block research. The time has come when the MCA should be encouraged to take a similar approach and not to use their powers in an arbitrary way to delay and disadvantage the UK research effort.

2. The relatively slow pace of gene therapy research in the UK compared with the United States is not only for regulatory reasons, but also because of poor co-ordination between university based medical research and pharmaceutical companies. A great deal of venture capital has gone into this area in America and almost none in this country. Since there will almost certainly be great human and commercial gains from this new chapter in human treatment, every effort should be made to encourage a positive attitude to this work and early collaboration between drug companies and research workers.

Letter from Professor Peter Day, The Royal Institution of Great Britain (HGC3) (9 November 1994)

Thanks for your letter inviting my views about issues relating to human genetic research, especially those impinging on public awareness and education in these matters.

Two separate questions arise: to what extent is the public educated in the facts about genetic research and its possible consequences, and how can the concerns which arise (either through knowledge or ignorance) be addressed?

On the first question, clearly there is room for much more effort to educate the public about what is being done, what may become possible over a period of years and finally what will never be possible. Where mass education is concerned, one turns at once to television because of its ubiquity and potency. Government agencies cannot (thank God) dictate to the BBC or ITV what matters they focus on. Nevertheless, government has a role in pointing up the issues of importance to society in such a way that mass media are persuaded of themselves about the rightness of giving them prominence. To achieve that, their attention has to be drawn (not in a

minatory, but certainly in a decisive way) to the facts and their consequences. It seems to me that, in an extended role, POST has much to offer in this respect.

Secondly, how can public concerns legitimately be orchestrated and addressed, when the knowledge necessary for informed discussion is present? Here, I believe the model of the 'consensus debate' pioneered by the Science Museum has a great deal to offer. Questions arise, however, about the means of choosing participants in such discussions, and the status of the organisations acting as convenors. On the first of these points, it must be clear that while self selected audiences will inevitably be partisan, groups selected on corporatist lines will equally carry no conviction. On the second, I believe it of the greatest importance that the organisation of such debates must be seen as independent of any government orchestration. Hence, they have to be convinced by institutions quite separate from government. Naturally, among these I would point to such historical organisations as my own and the British Association, distinguished as they are as media for disinterested debate on scientific issues over the last century and a half. I am quite sure that both would be ready to take on a role as ventilators and even arbiters of public debate, not only on genetic research, but other equally important matters of public debate.

Memorandum from The Revd. Canon Dr Keith Denison, The Church of Wales Diocese of Monmouth (HGC6) (19 November 1994)

I have been asked by His Grace the Archbishop of Wales to respond on his behalf to your invitation to comment on the issues raised by your Press Release on Human Genetics, dated 3rd November 1994.

You ask for an indication of the way in which respondents inform themselves on developments in science which might lead to ethical difficulties and how these might be addressed. I am privileged to be the sole Welsh, and Churches', member on the UK Gene Therapy Advisory Committee, and as such receive detailed information not only about each research protocol but also about developments elsewhere. Further information is gleaned from both generalist publications like *New Scientist* and *Science,* and specialist journals. For example, although at present only somatic cell rather than germ-line gene therapy may be approved in the UK, it is important to be prepared for the reopening of debate on the latter, and in this regard I found most helpful an article on its possibilities and problems in *Science* Vol 262, 22 October 1993, on *Germ-Line Gene Modification and Disease Prevention: Some Medical and Ethical Perspectives,* by Nelson A Wivel and LeRoy Walters. That article scrutinised the ethical arguments for and against and concluded that "Germ-line modification could ultimately be regarded as a technology too dangerous to undertake or it could be viewed as a justifiable approach to preventing certain forms of genetic disease".

My initial response to the key questions posed in the Press Release is as follows:

(1) The current state of the science is one of rapid development largely funded and motivated by the multinational drug companies. From the companies' perspective the major factor influencing development must be the profit motive; from a researcher's perspective it must be the prevention and eradication of genetic disease, with also, no doubt, a concern for academic achievement. Development of the science will be accelerated by the formation of a gene therapy "superclub" concerned with combatting major diseases such as cancer, cardio-vascular disease and disorders of the nervous system (Andy Coghlan, *Gene superclub signs up top players, New Scientist* No. 1952, 19 November 1994).

(2) The driving forces are public health, profit motive and academic reputation.

(3) There are risks as well as benefits, which is why all gene therapy protocols need thorough vetting and continuing quality assessment. The risks of unpredictable side-effects in germ-line gene therapy seem such that it should not be undertaken, since such effects will be perpetuated into future generations.

(4) The social, ethical and medical implications need careful exploration. Informed patient consent is crucial and adequate patient information and independent counselling are of paramount importance. We need also to remember that the human gene pool belongs to humanity as such and raises the question of the nature of humanity (for the Judaeo-Christian tradition, what does it mean to say that mankind is made "in the image and likeness of God"?)

(5) Genetic research and its applications are clearly being financed and managed primarily by the major multinational drug companies: Government health departments, and the insurance industry, also inevitably have a keen interest in such developments. It will be difficult to establish the full costs of such research. As to whether the level of investment is appropriate to the potential outcome, that is a matter of subjective judgment on which there will be wildly differing perceptions.

(6) Research is currently regulated by the Gene Therapy Advisory Committee, protocols having first been approved by the Local Research Ethics Committee. LRECs differ markedly in their degree of scrutiny,

and there is urgent need for a common standard of quality control. GTAC, under its Chairman, Professor Dame June Lloyd, and with a competent and efficient secretariat, is coping well with the current workload, but to secure public confidence and accountability, its meetings should in principle be open to press and public (subject to the protection of sensitive commercial information).

Letter from Mr P Falder, Managing Director of CP Laboratories (HGC7) (24 November 1994)

Thank you for sending me a request to submit comments to the committee enquiring into Human Genetics and Biotechnology.

I must preface my remarks by stating that I am no more qualified to comment on moral issues than the next man, neither can I claim to be a professional scientist.

Where I think I may be able to offer some useful insight is from the commercial viewpoint.

As a participant in the biotechnology area for some time I feel that all private spending and a lot of effort paid for out of public funds is driven by the prospect of personal gain!

The comment about publicly funded research may seem strange but many publicly funded advances are developed by the scientist for their own personal gain via them either setting up their own private company and continuing development to a commercial product, or by transferring into the private sector at an opportune—for them—moment.

The inevitable conclusion to be drawn from this is that regulatory regimes should err on the side of caution. This is because with the stakes so high—both for corporations and individuals—there is very little that people "will not do".

Indeed people in my position are constrained by their training to nakedly pursue profit maximisation. To use an example: concern for recycling and the environment is all very well, and as an individual I welcome it, but if a chief executive is dismissed at the AGM because of an indifferent profit record he does neither himself, the company nor the environment any good at all!

Turning aside from this examination of the dark side of human nature and commercial realities there are several fairly uncontroversial points that Her Majesty's Government should try to address. The idea that naturally occurring gene sequences and genes can be patented is preposterous and should be stamped on. I view this attempt by certain US scientists and corporations with greatest outrage. This is of course a quite separate issue from custom made genomes synthesised by inserting sequences that could never arise in nature—at least not in any meaningful human timescale.

Finally, if you would allow me to indulge in one highly personal comment; I feel that an individual's genome is their own personal property and there should never be any pressure from whatever quarter for it to be revealed, used against them or to be used as an excuse for them—much as I would like to be able to abdicate responsibility for the less attractive aspects of my behaviour!

Memorandum from Friedreich's Ataxia Group (HGC8) (22 November 1994)

On behalf of the Ataxia Group I would like to make a brief response to your enquiry. The questions are necessarily wide and complex and it is beyond our resources to give lengthy or researched replies. However, I know that the Genetic Interest Group is going to give the matter considerable attention and for much of the response I would refer you to their submission on behalf of voluntary organisations concerned with genetics.

1.3 What are regarded as insuperable moral problems may well be culture based—what may be unthinkable now may not be so in twenty years time. Geneticists should certainly think more widely than immediate goals and consequences, as should a range of other people. Thus some research could, and probably should, be prohibited now, but this may change.

1.4 Genetics may well lead initially to a deterministic view of human behaviour—increased understanding will ameliorate this in the same way that environment was an excuse for most anti-social behaviour. Common sense, in the end, will show that we are multi-factorial. Improving the world generally is probably not a good idea—improvement tends to be a subjective concept.

1.5 Germ line intervention is worrying in the sense of it being used to "improve the world" rather than improve the lot of individuals. If certain disorders could be eradicated then I fail to see the problem—the trouble is trying to draw the line between that and other "altruistic" interventions.

2.1 Public knowledge of genetics has increased considerably—few days go past when there is not some reference in the media. However, for those not personally involved the understanding is necessarily very limited. Schools in particular have a chance to make an impact—much of genetics is still taught on the plants and animals level.

2.2 There is undoubtedly some anxiety about genetic research—some, as above, may be justified. Other aspects that may lead to treatment need to be portrayed positively.

2.3 There is a belief that knowledge will inevitably lead to a solution—perhaps it will, but hopes need to be realistic and it is irresponsible of researchers to give false hopes of speedy answers.

2.4 As stated above, genetics may well be used as an excuse in the same way that environment has been. Justifications for reductions in social programmes are usually pragmatic anyway.

2.5 Human behaviour, ethics and beliefs can be seen to reflect the larger and smaller culture and social context—genetics may be proven to be a part of this and/or to affect particular individuals. Perhaps the main issues are ones of differences rather than good or bad according to who is judging.

3.1 Routine medical services should include information on a genetic diagnosis. The amount of research, of course, will depend on what is being done about that particular condition at the time. The genetic implications are usually explained at the time of diagnosis, but the information may be incomplete or even erroneous. This is probably due to a number of factors—rare disorders where non-specialists are giving the diagnosis, the rapid development of genetic knowledge and interventions, the number of disorders which are not referred to geneticists.

3.2 As above.

3.3 Genetic information should be confidential and tests should not be requested by anyone other than the person concerned. Genetic testing is different because it is information about a currently healthy individual—other medical tests usually concern existing conditions. Currently, also, testing may not give information as to the age of onset of the condition and to be properly interpreted insurance companies etc. would need to have huge amounts of complex data which would need updating frequently.

3.4 Population screening is appropriate when a disorder is sufficiently common and/or serious to warrant the cost and anxieties necessarily involved. Obviously, if treatment is available then screening is more than justified. However, for serious conditions with no treatment, the option of a termination would be beneficial to some families. The issue of informed choice is crucial, together with counselling when options are being considered AND after decisions have been taken.

3.5 Screening for diseases which are certain to manifest themselves, and screening for predispositions are different. The availability of screening for a number of disorders may become routine, but the decision to be screened should always be one of informed choice. As above, people need to be protected from discrimination by making the information confidential until, or unless, the disorder manifests itself.

3.6 Genetic information about partners would be extremely useful in cases, in particular, where some one already knows themselves to be a carrier of a recessive gene. Where, however, there is no prior knowledge, there would have to be considerable input into explaining the information and its implications.

In addition to the above points, I would like to draw attention to the differences between childhood and adult onset conditions. Information about the former may be helpful, for the latter it would intrude on the right of a person to decide for themselves as to what information they wanted. The Genetic Interest Group is currently working on a document on this subject.

Memorandum from Professor John Bell, Nuffield Department of Clinical Medicine, University of Oxford (HGC10) (23 November 1994)

I am writing with regard to the Science and Technology Committee's enquiry into Human Genetics. It would take a considerable length of time to discuss this in complete detail and as my colleagues and I here in Oxford are preparing a paper for Michael Peckham on this subject, I will only make a few points in this communication. The first and most important point is that this field is moving extremely quickly from a scientific point of view, and many important ethical and practical questions will need to be addressed in the very near future. In the last six months our programme in Oxford alone has generated new genetic linkages in asthma, diabetes and hypertension, and the recent publicity surrounding the cloning of the breast cancer locus I think highlights the difficulties that we will rapidly get into if we do not focus on some of the potential problems. In this country there is no question that the major motivation for the research to characterise common disease genes is to attempt to better understand the mechanism by which diseases occur, and if possible identify novel therapeutic interventions. This data should, however, also allow us to stratify populations according to risk and to concentrate our ever decreasing health care resources on the individuals most likely to benefit. In North America there are no major academic programmes such as the one here in Oxford and most of the science is being driven by biotechnology companies. Their motives are a great deal less clear.

It is likely within five years many disease genes for common human diseases will have been identified. These observations may provide remarkable new insights into the mechanism of common human diseases and may also provide an approach to defining disease more by their mechanisms than by their phenotype. This will have important implications both for optimising therapeutic interventions, but also may help epidemiologists to understand better how the environment interacts with our genetic background to create many of these diseases. One would hope that this would not only lead to the development of new drugs based on a firm understanding of the pathophysiology of many conditions which remain obscure from this point of view, but also may allow a more appropriate application of drug therapy to individuals. For example it should be possible to identify which patients are likely to respond to any given single agent for hypertension in a more precise way and hence save large amounts of money using inappropriate drugs in patients. It should also be possible to use this information to predict which patients are likely to respond badly and develop complications from particular therapeutic agents. In addition it should be possible to identify people at very high risk of particular diseases and initiate therapy early, hopefully preventing the disease from developing fully or resulting in serious disability. There is considerable hope for example that this genetic information will allow the identification of people at high risk of juvenile diabetes. A small sub-set of the population could therefore be studied for evidence of an immune reaction to the pancreas and if this was present they could be treated early before they develop the full symptom complex of diabetes. A similar approach is already being used in America for the management of patients with early arthritis. A particular set of genes confers on this population an extremely high risk of developing rheumatoid arthritis. Patients in whom a diagnosis is uncertain who have this genotype are now being treated aggressively as if they have rheumatoid arthritis, and this appears to produce a remarkably improved natural history, with fewer joint erosions and disability after several years follow up.

The major issue that needs to be addressed now, however, is how we will use this information to apply sensible and helpful screening programmes to the population. Screening for disease in "susceptibility" genes is quite different than screening for genes that are fully penetrant and invariably cause disease. Nevertheless the benefits of such screening could potentially be enormous in allowing us to focus our health care resources on individuals most at risk, and also utilising them to best effect based on an understanding on disease mechanisms. There are many issues here such as who should be screened (whole populations or only particular at risk groups), whether one could permit the screening of children, whether one needs to have an intervention to permit screening for disease and how would one supply the necessary counselling when one begins to screen very large numbers of people for common disease genes. It seems clear to me that this is going to be a very substantial problem and that in the end, although one can think about methods for focusing counselling efforts on particular sub sets of the population, what is needed in the long run is a much more aggressive approach to educating the population so they are in a position to better understand what these evaluations actually mean. A distressing lack of understanding of biology and genetics in the population will not help us apply this important information to populations.

The issue of screening will have many benefits in terms of application of health care resources and development of new therapies, but the other important issues to be considered are the maintenance of confidentiality of this information and the rights of both insurance companies and employers to get access to genetic data. The role of insurance companies in this formula is extremely complex, but I suspect that this will lead to a very considerable re-evaluation of the role of the insurance industry, for if they become able to much more accurately predict risk of a large number of diseases in the population, the stratification of their premiums in response to this will lead to a large disenfranchised population. This obviously has very serious implications and needs to be considered carefully.

As an illustration of many of these points I should leave you with the example of breast cancer. It seems inconceivable now that the Health Service can continue with a national mammography screening programme for breast cancer without serious consideration of the role of genetics. This will, in the first instance, involve screening with the BRCA 1 locus, but in order to do this successfully one must have in place an effective

counselling system to advise women who are positive for the test. This raises a number of issues, as individuals who test positive may require very large amounts of counselling. The issue of whether the mutation and sequence of this gene can be patented and a licence fee levied is also, I think, important to consider. More complication, however, is the ataxia telangictasia locus which is probably also involved in susceptibility to breast cancer. It has been estimated by Michael Swift and his colleagues that this locus, which encodes a gene that may lead to increased radiosensitivity of cells, when present in the heterozygote state leads to an increased susceptibility to breast cancer. Estimates suggest that as many as 5 per cent of individuals with breast cancer may be AT heterozygotes. I have just returned from the United States where it appears that this locus has now been cloned. If this proves to be the case it will again throw screening programmes into substantial disarray. If mutations at the locus are associated with increased radiosensitivity and with an increased risk of breast cancer, then it would seem extremely unwise to persist with a breast cancer screening programme without first testing for mutations at this particular locus. A failure to take such precautions might lead to substantial liability in the future. These are a few examples of the sort of difficulties we are going to rapidly encounter as information about disease genes begins to emerge.

I would urge the committee to consider carefully all of these issues. Seldom has an area of biological science had the potential to impact so broadly on each of our lives and how we proceed needs very careful consideration. The Government must also take seriously its responsibility for ensuring that the ethical considerations have been carefully considered and the studies on how this technology is applied to populations have been carefully performed. We are very adequately funded, at least in Oxford, to generate information about these disease susceptibility loci. The mechanisms by which to obtain support for the application of this information within the context of the Health Service is less obvious.

I hope these comments have been helpful to you. I could provide more detailed information if you thought it would be appropriate.

Memorandum from Dr P Little of the Imperial College of Science, Technology and Medicine (HGC11) (28 November 1994)

PERSONAL BACKGROUND

I am replying to your request to submit evidence to the Science and Technology Committee's inquiry into Human Genetics. I was a member of the OST expert working subcommittee on the Human Genome Project and am a member of genome analysis advisory groups to the MRC and the BBSRC and to the Leukaemia Research Fund and the Wellcome Trust. I am replying in my personal capacity as a Reader in Molecular Genetics at Imperial College where I am actively researching within Human Genetics and the Human Genome Project and teach at all levels.

I have focused my replies to a limited subset of questions posed in your covering paper sent to me on 7 November. The numbers of my answers refer to the question numbers in this list.

1. *General ethical and regulatory*

1.1 An understanding of the way genes work is not central to defining the regulation of the uses of this information. We have very powerful mechanisms for regulating genetic research in place already and these are adequate within the UK. I do not see that additional, new, information will produced qualitatively new problems and would anticipate that we will simply expand our understanding of human disease and physiological differences: the problems that may be associated with such information will be adequately handled by existing regulatory mechanisms. Another way of putting this point is to suggest that new information will increase the number of times that guidance will be required without changing the quality of that guidance.

1.2 I am strongly of the opinion that the guidelines and regulatory mechanisms in place within the MRC and other Research Councils, and within the major Research Charities, are adequate for the control of the acquisition and use of genetic data: I am less sanguine about the activities of privately owned enterprises which are free to operate outside of some of these guidelines. Peer group review of research council and charity funds remains a powerful method for exposing potential conflicts of interest and I am a firm believer that this must remain a central mechanism of control.

1.3 I would only state that I do not accept that scientists could operate a "hidden agenda". I do not see how this could come about within the publicly stated mission goals of the MRC, BBSRC and charities: to assume that there is such an agenda would require covert and wholesale flouting of stated aims at a scale that would be unprecedented in an open and democratic society such as ours.

2. *Public awareness and education*

2.1 and 2.2 The general awareness is low and frequently wildly overestimates scientist's ability to understand and, more crucially, manipulate our inheritance. There is a real interest, often tinged with a general unease based upon this overestimate of scientific powers. There is a much wider acceptance for using genetics to aid the treatment of genetic diseases. The only counter to the unease is education through the mass media and through the school system. The construction of a systematic program to foster public awareness of the issues would be an attractive mechanism for increasing some degree of understanding and this in part already exists: a more specific focus on genetics would be useful. The relative decrease in the public estimation of scientific endeavour is a factor contributing to the difficulties and this is a general political and social problem.

5. *Research*

5.1 and 5.2 By understanding the structure of all our genes we lay down an "envelope" of information which must contain the basic building blocks of the cellular machinery of a human being. Given there are some 65,000 genes, we have no hope in the near future of understanding the contribution of all of these to human life. The knowledge of the structure of all of our genes will provide the raw information for future generation's studies. In the immediate term, we will be able to use the information in a very specific way: this is because genes are frequently rather similar—so called gene families. If we identify the properties of one member of the family, we can often guess at the properties of all the rest of the family members. At present, we have no way of knowing a gene was a member of a family without laborious and often unsuccessful experimentation: knowing the structure of all our genes gives us access, with certainty, to the information of what our cells are made of with no gaps in our coverage. This is a key role of the Human Genome Project.

It is a massive step from identifying a gene to understanding what role it plays in the living process. This is the area where medical and basic research interact most vigorously, in particular in the identification of the causes of genetic disease. The specific value of knowing the position of a gene in humans—the "map" of human genes, is that it is an immensely powerful aid, indeed frequently the only clue, to identifying the cause of complex genetic diseases such as some cancers, heart disease and diabetes. Once we know causes we can work to design therapies.

The advantage of mapping only expressed genes is purely economic—only 5 per cent or so of human DNA (the chemical constituent of our genes) is actually involved in genes but the remainder is the space between genes. A program of work aimed at this 5 per cent would be 20 times cheaper than one aimed at all human DNA. There are several reasons why we should be cautious in accepting this simple economic argument.

- It is difficult, expensive and inefficient to identify expressed genes. Costs will not be quite so reduced as might be anticipated by a superficial view.
- Technically, the project will necessarily be incomplete—we have no methods for identifying all genes in humans except by analysing all human DNA.
- More importantly, the space between genes frequently contains the DNA that controls when and where a gene is to be used in humans. Most genes are only needed in a few tissues at particular time points in our lives. An understanding of when a gene is used is very important to understanding its role, as important as understanding its structure. This is because a gene being used at an inappropriate moment or in an inappropriate cell type is a frequent cause of genetic disease and, in particular, cancer. We cannot establish the structure of controlling DNA by analysing only expressed genes and this is why I am personally not a strong supporter of proposals that this should be the sole way forward.

In the UK the MRC has both expressed gene programs and whole DNA programs and this is very appropriate.

5.3 We really do not know the answer to this question. We all accept that identical twins look very similar which argues for a measure of influence of our genetics on our physical characteristics. Major controversies over this area are founded upon simplistic measures of human achievement and these premises are rejected by most geneticists (the supporters of these arguments are frequently political theorists or psychologists). As a geneticist, I can simply point out that in most cases we know far too little about what makes up a human being to be able to explain how or why our genetic composition does or does not influence complex characteristics. In some very simple cases, the contribution is more apparent.

5.4 We only have a general description of the organisation of most coding information in humans: in some areas, certainly less that 1 per cent, we have a more detailed understanding. There is no reason to suppose that there is an exceptional danger associated with gene therapy: experimental studies and work on isolated cells both support this view. Technically, we can target the gene therapy to particular sites in the human genes which would not be deleterious so I would argue that in the longer term this will not be an issue.

5.5 I believe that the balance of funds between human genetics and biomedical research is by and large correct but that the overall funding levels are inadequate: if we are to compete on an international scale we need an injection of funds for both genetic and non-genetic research.

6. *Evolution*

I find all of these questions somewhat surprising. They are based upon a short term view of evolution whereas this is inevitably a very long term, multi-generational process. The history of the twentieth century, in particular, shows that political, economic and military actions have an immensely greater impact on human populations then the activities of genetic doctors. The idea that medical intervention in the genetics of humans can be equated with the effects of these huge fluctuations in the human environment is extraordinarily naive. It has been estimated that over 180 million humans have died in the course of twentieth century wars. The associated disintegration of civic and national organisation has had a far more potent effect upon human survival that any amount of highly technical, expensive and numerically limited genetic manipulation. The impact of genetics should not be confused with the impact of general medical science, which has had, and continues to have, a massive effect upon mortality and morbidity statistics. I would argue that genetics affects hundreds of people annually and until it effects tens of millions, these questions are without scientific foundations. The prospect of genetic intervention at this scale is in the realms of science fiction.

Memorandum from Dr Anne McLaren The Wellcome Trust/CRC Institute (HGC12)
(28 November 1994)

1. GENERAL ETHICAL AND REGULATORY

1.1 Information about and understanding of the way in which genes work is increasing rapidly but is still very fragmentary. Until we understand more about how genes work we will not be in a position to make much use of the information at the descriptive level that is emerging from the Human Genome Mapping Project. In particular, without more understanding of how genes work, it will not be possible to raise the productivity of plants and animals by applying novel genetic technology to those characteristics of economic importance which have already responded maximally to natural and artificial selection. It will also not be possible to devise rational approaches to human gene therapy. Trying to cure a gene defect in ignorance of how the normal gene works may lead to unexpected and undesirable consequences.

1.2 MRC, Wellcome Trust and ICRF are fully aware of the ethical and social importance of human genetic research. Local Research Ethics Committees play a part in ensuring that any such research is conducted ethically, but funding bodies also review ethical aspects. Through its Genetic Approaches to Human Health initiative, MRC was instrumental in involving social and behavioural scientists in considerations of the impact that prenatal diagnosis, genetic screening and gene therapy might have, and how such procedures might be introduced so as to increase human welfare, rather than producing undue anxiety or other adverse consequences. MRC and other funding bodies are also concerned to promote public understanding of human genetics. On the other hand the funding bodies on their own are not and should not be responsible for dealing with the social consequences of human genetic research. *Ad hoc* committees such as the Clothier Committee that considered gene therapy, and non-governmental organisations such as the Nuffield Foundation's Bioethics Council that produced a recent report on genetic screening, have an essential role to play; but the recommendations that they make have to be taken on board a governmental level.

1.3 Research and the acquisition of knowledge, should not be prohibited on account of its possible consequences, provided of course that the research is carried out in an ethically acceptable manner. It is in the application of research, the way in which the knowledge is used, that moral problems arise and regulations, surveillance or prohibition may be required. It is a truism that all important scientific advances may be used for good or ill. Most geneticists do think more widely that their immediate research goals and often adjust their goals accordingly. By virtue of their expert knowledge, they have a special responsibility for seeing that their work is applied for the good of society, but they have no more and no less right than any other citizen to decide what society wants. I doubt there are any "hidden agendas", but it is important for scientists to be as open about their research as possible, and to seize every opportunity to explain to the public what they are doing and why.

1.4 People have been improving the world through genetic interventions by plant and animal breeding for millennia and should continue to do so. Genetic determinism is undesirable and scientifically ill-founded, since human behaviour like all other characteristics, is influenced by both nature and nurture, genes and upbringing and environment.

1.5 Through medical and social interventions, we are "playing God" all the time. If God created Man "in his own image", this is not surprising. The problem with germ-line intervention is that we not only do not know what side effects it might produce, but we also do not know and cannot know what view future generations would take of those effects.

Memorandum from Professor F Sanger (HGC13) (30 November 1994)

1. General ethical: When the possibility of genetic engineering was first considered, several scientists in the field were worried that there could be dangers in working with re-arranged genetic material, and it was mutually agreed to have a moratorium on such work until suitable preliminary experiments were conducted. When the work—largely on micro-organisms—started, strict restrictions and a code for various levels of containment were instituted and rigidly adhered to. As more work was done it became clear that there was little danger and that the restrictions were needlessly stringent. At the time the press heard about the work and, hoping for something sensational, tried to persuade the public that genetic engineering was dangerous. This resulted in various countries setting up their own standards and codes of practice, many of them over-restrictive, and some are still in use today. I think this illustrates that scientists are responsible people and do think "more widely than their immediate research goals." It is the press that does not always think beyond their objective of selling more newspapers.

1.6 The human genome has developed over the ages and is ideally suited to its function. Its structure remains stable and on the whole is well able to protect itself. Any intervention could only affect individuals and their descendants by altering small bits of the DNA. This is however a process that has been going on all the time in nature and is an essential factor in evolution: good changes have been preserved and bad ones eliminated. Thus any gene therapy would be no different from the natural process except that it could be planned to bring about only "good" changes. Genetics is not a new science. The general principles of inheritance have been known for almost a century and used extensively to alter the chromosomes, and therefore the characteristics, of animals and plants by planned breeding. There has been no general public opposition to this and no central regulation seems to have been required. Similar techniques could equally well have been used on humans, but, other than in nazi Germany, have not. The reason for this is that they are not socially acceptable. I think the same restraints would apply to any possible manipulations of human genomes. The more sensational press sometimes envisages the possibility of creating a race of supermen (or even monsters) by genetic manipulation. This is far from possible at present, but one could envisage that a gene giving increased mental ability or bodily strength might be discovered in the future and that it might be feasible to insert it in an individual's DNA. It seems to me that this would be for the individual to decide on and that there would be no need for a more central control—though we would have to know much more about gene therapy than we do now.

5. Research (human genome): The sequence of the human genome is essentially a blueprint containing the complete instructions for making a human being. In order to mend a piece of domestic equipment (for instance) it is desirable to be able to study the instruction book. For humans we don't yet have the instructions and this has been a great disadvantage in medicine. We now have the possibility of reading the instructions and I think the effort to read the sequence and understand its meaning is well worthwhile. Besides medical problems it is already throwing light on more fundamental biological aspects such as control and development. A great deal of effort is already being devoted to this problem in many countries and there is a good prospect that it will be completed in the not too distant future. In most laboratories the results are made public, and I feel it is important that there should be no secrecy about it. Humans have a right to know about themselves. A more difficult problem is in regard to any one individual's genome (3.3). There are of course differences in the genes of individuals, and it is these that account for our specific characteristics. It should soon be possible to identify what defective genes, and maybe other characteristics, an individual has. It has been argued that such information would be useful to prospective employers and insurance companies, but whether they should be given these details I don't know. In the near future the main medical applications of the human genome project are likely to be in genetic diseases. Many of the genes concerned will probably be located and the defective gene detected. Much of the present research is devoted to somatic cell gene therapy; i.e., giving the patient a normal gene to replace or supplement the defective one. This seems already to be possible but is somewhat limited in its effects. This type of treatment is probably only temporary and is in principle no different from normal medical treatments, and so it should be subjected to the same regulations. The other possibility is germ-line therapy—that is replacing the defective gene in the germ-line of the patient with a normal gene. This would ensure that none of the patient's offspring would have the disease. If this type of treatment became possible it would be a way of eliminating these diseases, and is therefore being actively worked on. Unfortunately there has been some opposition to this idea. People have argued that it would alter the entire human race and that the human genome should not be interfered with. This is of course nonsense as it would only affect the patient's own descendants and would be highly beneficial. Of course such experiments on humans should not be attempted until adequate preliminary work has shown that they are possible and there are no deleterious side-effects. It is difficult to guess how long it will be (or indeed if ever) before this is possible. New pieces of DNA can now be inserted into chromosomes, but in order to work properly they should be inserted in the correct position where they would be under the control of the normal regulatory factors and would behave like the normal gene. If they are in the wrong position, they would not be correctly controlled and could produce too much or too little of the protein, and at the wrong time. They would also be expected to affect the activity of other genes, giving rise to undesirable side-effects.

Evolution has been brought about in the past by a process of severe competition between species, an important factor being the elimination of the weaker and unfit species. In modern society this factor has been almost completely removed and efforts are made to ensure the survival of the unfit. Thus it is unlikely that human evolution is proceeding in a positive direction. I think this has to be accepted, but perhaps germ-line therapy will make it possible to plan further evolution in a positive direction, and I consider this should be encouraged.

Letter from the Genetic Research Instrumentation Ltd (HGC14) (30 November 1994)

We were interested in the scope of the enquiry into the issues raised by human genetics research. GRI are specialist suppliers of instrumentation for cellular and molecular biology, the basic science for the biotechnology industry and which is used for genetic manipulative experimentation.

Whilst not being involved with day to day research and, therefore, unable to offer any view on the ethics of the research project, we do have an interest in the economic benefits of this technology.

The accent of your enquiry point 4.5, appears directed to drugs or related biochemicals produced as by-products of the research which may be used in the treatment of human illness.

There is, however, a considerable industry in the research and development of a wide range of instruments used in the research projects and in the aid to diagnostic systems based on genetic fingerprinting and mapping.

In particular, the development of DNA Amplification, Programmable Thermal Cyclers (used in the Polymerase Chain Reaction methods) will be considerable in the future for use in quality control within the food industry, a whole new approach to diagnosis of both infectious and genetic diseases as well as in research programmes for gene mapping and sequencing.

In the UK alone, we see a demand in excess of 500 machines per year at present, these being valued at between £3,000 to £4,000 each, rising by some 10 per cent per annum for the next five years. The diagnostic test kits and associated biochemical reagents will be more than 10 times this value per year as consumables.

From these technologies will come new analytical software for identification of sequence patterns allied to bacteria or protein identification, molecular weight determination, measurements etc., which in turn will lead to development of data management systems.

We foresee multi million pound development of new instruments well into the future, particularly with automation and use of robotics for diagnostic application.

Trusting that this information may be of use to you and we look forward to studying the findings of your enquiry in the future.

Memorandum from Professor T M Dexter, Paterson Institute for Cancer Research, The University of Manchester (HGC15) (24 November 1994)

INTRODUCTION

Some human diseases arise as a consequence of a change (called a "mutation") in a *single* gene which is inherited from one or both parents who themselves may show no symptoms. Examples of this include Gauchers Disease and Hurlers Syndrome—both of which are due to a defect in the ability of cells to produce a functional protein that is essential for certain critical activities that some cells need to perform in order to fulfil their normal roles. Once the genes encoding these proteins have been *identified* then

(a) non-affected individuals who carry the mutation can be *recognised* and *counselling given* as appropriate;

(b) individuals *at risk* of development of disease can be distinguished and clinical monitoring procedures put in place;

(c) knowledge of the *function* of the gene product within the cells permits the development of therapeutic strategies, such as enzyme (protein) replacement therapy in the case of Gauchers Disease—a procedure in which patients are treated with a genetically engineered active protein that is taken up by the tissues and

(d) direct gene replacement (rather than "product" replacement) becomes a real possibility.

The advantages of gene replacement therapy are twofold. First, this will eventually become a "one off" procedure with the associated benefits for quality of life of affected individuals. Second, "product" replacement therapy is a life-long therapy with very significant cost implications—not only for the product itself, but also for the medical and other personnel required for administration and monitoring of the product and the patient. Thus, a "one-off" gene replacement therapy may well lead also to substantial financial savings in the medium to longer term.

Other known diseases occur as a result of mutations in several genes (these are called polygenic diseases)—an obvious example being cancer. Naturally, because of their polygenic nature, these diseases pose much more formidable problems than the single gene disorders. Nonetheless, for any one disease, relatively few genes are likely to be critical, and knowledge of where these genes are on the chromosomes, combined with identification of the product and the function of these genes, immediately opens avenues to diagnosis, risk-assessment and therapeutic interaction.

In answer to the specific questions:-

1.1 Considerable in-roads have already been made in identifying how expression of individual genes is regulated is specific types of cells. Naturally, this does not apply to all genes (most of which still remain to be uncovered). Nonetheless, paradigms have been established and methodologies have now developed to a state where I feel confident that decisions regarding their use and regulation can be made by the appropriate regulatory authorities already in place.

1.2 Yes. The scientists and physicians working in this area, in addition to their funding bodies, are well aware of the ethical and social implications of their work and great care is being taken to have full and frank discussions at every level.

1.3 Society always has a right to declare some topics "off-limits"—provided that their choice is based on facts and reasoned argument rather than on hearsay and prejudice. However, as I sure the Committee appreciates, ethics are not fixed in stone—and what is deemed to be unacceptable now may well be accepted by society in the future. Because of this, I believe that it is particularly important to keep channels open for discussion and re-evaluation of the more controversial issues.

In my experience, geneticists *do* think more widely than their immediate research aims and, because of this, it is also important that they continue *contributing towards* the current debate. To my knowledge, they are *not* pursuing a hidden agenda—and to suggest otherwise is a gross injustice to their integrity.

1.4 We are clearly influenced by the genes we inherit—to suggest otherwise would be naive. Continued research *may* lead to identifying individuals at *risk* of a particular aberrant pattern of antisocial behaviour—but it is highly unlikely (because of the multiple genes involved and because of the undoubted influence of the environment) that genetic interaction would be countenanced in such individuals—at least for the foreseeable future. Indeed, recognition of "at risk" individuals—and the importance of the environment—may well encourage social changes rather than genetic intervention.

1.5 Individuals who are suffering disease as a consequence of mutated genes inherited from their parent did not "give their assent" to the disease. In principle, provided that the safety and ethical issues have been widely explored, I see no objection *in principle* to germ-line intervention. Naturally, people with religious beliefs *may* view this differently and their views should be respected. However, whether or not their view should be *imposed* upon society as a whole is a matter for society to resolve. What I *can* say, is that people working in this area (including myself) are well aware of the implications of germ-line manipulation and would welcome a continuing debate on the benefits (or otherwise) of such interventions to society.

1.6 No patents allowed!

2.1 Every mother, father and child with whom I have discussed genetics has a major interest in the topic. Unfortunately, their *knowledge* is (at best) modest and their understanding based more often on prejudice rather than on fact. Even the "chattering" classes are fairly ill-informed. However, this applies to science in general rather than genetics in particular—and several organisations (The Royal Society, the MRC, the Research Charities) have already recognised this and have the machinery in place to inform people of scientific developments. The major problem, however, is that the natural "targets" are the more educated sectors of society and steps should be taken to introduce the majority of people into the scientific debate. The Government has a major role to play here.

2.2 Yes. Some of this is justified (e.g., the possibility for germ-line intervention), but most suspicion arises out of ignorance of the nature of inheritance, the role of genes in disease and the many benefits that genetic knowledge can bring to society. Education is required here!

2.3 No. I sense no unreasonable expectations.

2.4 Yes. There is a danger (but see 1.4). If anything, however, it could be used to justify an *increase* (not a reduction) in spending on social programmes.

3. Genetic diagnosis of *major* diseases, such as cancer, is presently associated with research programmes. A major priority is to establish this as a *service* and Government funding should be made available for this via organisations such as the MRC, NHS. Several mutations in genes have now been identified that lead to "cancer" proness. At the moment, resources simply are not available for an adequate family screening programme to be established.

3.2 No.

3.3 I do not believe that a strong case can be made for *compelling* individuals to have a genetic test(s) prior to employment or for insurance purposes. However, if a genetic test *has* been performed, for whatever reason, then the onus should be on the individual concerned to provide this information to employers in cases where an underlying disease, or the risk of developing disease, impacts on current legislation regarding health and safety at work. Similarly, relevant information should be made available to insurance companies *provided that* such companies are seen to be fully conversant with risk-assessment for development of a particular disease. In the majority of cases, of course, insufficient information is available for them to do this analysis and—until this information becomes available—it would be unwise to make this compulsory.

The difference between genetic testing and "normal" medical tests is that the latter *identifies a disease* whereas the former (at least in many cases), only identifies individuals *at risk of developing disease.*

3.4 Population screening for genetic disease is only appropriate, I believe, *when preventative and/or curative measures are available.*

Clearly, there are major financial implications—but one sample (e.g., of blood) should eventually be sufficient for screening for all known genetic deficiencies. Obviously, the *cost* of screening may well be counterbalanced by subsequent savings in health care and working life.

3.5 The information should be treated as strictly confidential and *compulsory* disclosure limited to very rare circumstances (see 3.3). Provided that preventative/curative measures are available, I see no course for concern regarding possible discrimination. After all, we did not discriminate against diabetics—also a killer disease, before insulin was discovered.

3.6 Some, but very few people, would no doubt welcome this—but love overrides most prejudices!! and I do not believe that this will ever be commonplace.

4.1 Knowledge of the genes and their products will revolutionise drug development. In the past, drug development was largely empirical: once the "target" is known, a much more rational approach can be adopted.

4.2 "Gene" therapy offers the prospect of *cure* rather than continual treatment. Thus, although the *initial* treatment may be costly, a great deal of money will be saved in the medium to longer terms.

4.3 A great deal—but there is now more interaction between academics and pharmaceutical companies than ever before.

4.4 As always, we were slow to develop a commercial base in this field—and the UK only has *one* start-up gene therapy company compared with hundreds in the USA. We have become *averse to taking risks* and something clearly needs to be done if we are not to be left behind in this and related areas. This is not a fault of the regulatory authority—or of the UK academics who all too often see their findings being exploited elsewhere. However, unlike the situation in the USA, academics in the UK only very rarely consider starting up their own companies perhaps because of the personal risk and/or the perceived difficulties in raising the money to do so.

5.1 A map and sequence of the human genome will provide the database for present and future generations of academic and clinical geneticists. It will certainly aid in our understanding of population diversity, knowledge of polygenic diseases, identification of novel genes and their products (for possible therapeutic uses) and aid in the development of treatment strategies. Mapping *expressed* genes is a parallel approach of relevance to *specific tissues where those genes are expressed.*

5.2 Piecemeal studies tell us little about evolutionary relationships, coordinate gene expression and regulation. Perhaps the best analogy is the blind man and the elephant. When the whole is visible our perceptions will almost certainly be different from what they are at the present.

5.3 At the single cell level, the external milieu can clearly influence gene expression. I suspect however, that the question refers to the whole organism rather than to single cells or tissues and here the biological checks and balances ensure that there is much less scope for environmental influence, e.g., identical twins are remarkably "identical" even when raised in disparate households. Where the environment does have a significant role to play, however, is a) in terms of inducing in genes through exposure to genatoxic agents and b) in modifying complex polygenic characteristics such as behaviour.

5.4 Major advances have been made in understanding the organisation and regulation of genes. It is, of course, conceivable that genetic intervention may have unforeseen effects, but this is no more probable that saying that treatment of a patient with *any medicine* may have unforeseen effects. Indeed, because of our knowledge in this area and the stringent safety and regulatory procedures that must be adhered to, it can be argued that unforseen effects are much *less likely* than with other more "conventional" treatments.

5.5 Probably not. Again, a comparison with other countries such as Japan and the USA is a useful yardstick.

6.1 This is not my area: unable to comment.

6.2 This is not my area: unable to comment.

6.3 Evolutionary theory indicates that changes in the environment can have profound effects on evolution. I see no reason to suggest that humans will differ from other species.

6.4 At this stage, predictions would be foolish.

6.5 At the moment, probably none. What would be the final objective?

6.6 Natural variation ensures a diverse gene pool, including "bad" genes and "good" genes. There could well be circumstances, of course, where the "bad" genes *may* be useful (e.g., the sickle cell gene and malaria). Germ line manipulation would only be considered in circumstances where the "bad" gene is *obviously bad*—with no known benefits and where the "bad" gene (or the absence of a "good" gene) leads to severe physical/mental retardation, disease and premature death.

6.7 Absolutely not! There are very few pleasures left in life and I cannot imagine any support for this!

Memorandum from Professor B A J Ponder, CRC Human Cancer Genetics Research Group, The University of Cambridge (HGC16) (1 December 1994)

1. General ethical and regulatory

1.1 A major question to be tackled over the next 10 or 20 years is the identification of the genetic and environmental factors which *modify* the effects of disease causing genes. For example, the BRCA1 gene which predisposes to breast cancer, causes cancer in some women by the age of 30, in others by the age of 70, and in others not at all. To know why there are these differences would be helpful both for advising women about their risks, and also possibly as a route to manipulating the risk downwards. I think we are likely to obtain this information but it will require large-scale cooperative studies based on large population-based collections of cancer cases and families. At the moment it is quite difficult to get funding for such studies. In particular, the infrastructure of the NHS could be used to make such collections easier, if funding were available.

1.2 I think the policies are probably adequate: the problem is that no-one really has a clear idea about the best way to deal with many of these issues from the ethical or social standpoint. I am concerned that there is a proliferation of small research projects throughout the country when a more coordinated approach might be cost-effective. It seems to be much easier to get money to *assess* the clinics than actually to run them. Assessment is seen as "research", whereas the clinical service falls between the NHS, who won't take responsibility, and the charities, who can't afford it and don't see why they should.

1.3 I don't think geneticists that I know are pursuing hidden agendas. I think geneticists do think more widely than their immediate research goals, but they need help from others to sort out the social and ethical implications. Equally, the individuals who have the expertise in these social areas are often very poorly informed about genetics.

I think that putting certain research topics or techniques out of bounds could be counterproductive. No-one I know would favour germline manipulation in man, but the *mouse* it has been a very useful research tool.

1.4 Research into human genetics may lead one to take a more deterministic view of human behaviour than if one knew nothing about genetics at all, because a geneticist believes that part of an individuals behaviour and health is genetically determined. However, I think geneticists are keenly aware that there is rarely a one on one relationship between a particular gene and its effects—this gets back to the need to understand the factors which modify gene action which I mentioned in 1.1 above. My guess is that people will not try to improve the world through genetic interventions strictly, but through interventions which will modify the effects of genes. I think this is a crucial distinction. Coming back to breast cancer again, I cannot conceive of genetic intervention (by

which I mean manipulating genes) applied to the hundreds of thousands of women who are at inherited risk. I can imagine that such women could be given a tablet—such as tamoxifen or aspirin—which might considerably reduce their genetically determined risk, and that the target population for these interventions and the type of intervention would be determined by a genetic classification of risk.

1.5 In the situation where parents are at risk of transmitting a defined genetic disease to their offspring, it makes much more sense to me to perform genetic *selection*—that is, to identify and reimplant the good embryos (in almost every genetic condition there will be some of these), rather than trying to reimplant genetically manipulated bad embryos. If one is thinking about germline intervention in a sense of trying to breed a resistant strain of humans protected against some disease, I would have thought there were strong ethical objections to this, quite apart from our very limited understanding of what might result. Expressed briefly my main objection would be that this would be open to abuse as a route to deprivation of individual liberty and manipulation of the population by an authority.

1.6 I think the declaration and treaty should declare (1) that all scientific knowledge about the human genome and the structure and function of the genes should be freely available to the world community (2) but on the other hand genetic information which is specific to an individual should be confidential to that individual and not subject to disclosure on demand and (3) that while private investment has a part to play in funding research this should not lead to patenting of genes themselves, nor other patenting which obstructs the beneficial application of knowledge which arises from genome research.

2. Public awareness and education

2.1 The extent of knowledge of genetics amongst the public as a whole is extremely poor. Interest may be a little greater, but it is ill informed. My wife has recently conducted a research survey on this topic in Cambridge. School must be the best place to improve this, although current attempts (the new curriculum, etc.) seem remarkably ineffectual. I think this is part of a dismal picture of scientific education generally in this country. People are not taught science well on the whole, and there is not a sufficient proportion of the population who are used to thinking and evaluating questions in a scientific way. I think that science is undervalued and not sufficiently perceived as a worthwhile activity amongst the community. It is a sad commentary that in the five years that I have been running a fairly well set up lab in University of Cambridge, overall the most productive work has been done by overseas visitors rather than by English scientists.

2.2 There may be some anxiety and suspicion about genetics in relation to genetically manipulated food and "designer babies". In my own branch, the genetics of cancer, I find on the contrary an uncritical enthusiasm and expectation about the benefits that it is supposed that genetics can deliver in the short term. Both these types of misunderstanding can only be allayed by better education in schools and better communication about the topics in the media. (The Independent newspaper tries hard on science, but on Tuesday when it runs its science feature, it is interesting that the issue is headed on the outside "Media, Finance and Law" or some such—science isn't mentioned!).

2.3 I think there are unreasonable expectations amongst the medical profession and the public about the benefits that will come from identifying inherited predisposing genes for cancers. Again, the only answer is communication. I currently have an EC grant on which I have hired a lady who was previously an editor for a large publishing house, to write material for the public and GPs on this issue. I think it should be made easier to obtain funds and facilities for this sort of thing. I spend a good deal of scarce time talking to television and radio companies as well as newspapers. In many cases, their efforts to put across the science are first class. However, for the sake of a "good story" unfortunately many of them still indulge in hype. I suppose we can't stop this, we have to counter with more sober pieces, written by someone who knows how to communicate with the public as a whole.

2.4 I don't myself see a great danger that genetics will be seen as an excuse for socially unacceptable behaviour or to justify reductions in health programmes. I do think that the prospect of identifying people at inherited risk will *increase* the need for social programmes in education, support, and preventive treatment.

3. Genetic disease

3.1 At present much of genetic diagnosis (certainly in the cancer field) is carried out only in association with research programmes. The continuity between research lab and routine service is extremely unsatisfactory. Increasingly, the purchasers of health care demand evidence that a potential new service is beneficial. It is in the nature of genetic screening for late onset diseases such as cancer that it will take years to work out how best to use this information, what the implications of different mutations are, whether people benefit from counselling and genetic diagnosis, and whether we can use genetic information towards prevention. However, the research cannot even begin without a clinic base. The scope of this is a long way beyond the resources of the cancer charities or the MRC. It is absolutely vital that the government faces up better to its responsibilities for research at the boundaries of the NHS. The recent call for proposals for a total of £1,000,000 to be spread over 15

priority areas within cancer research is ludicrously inadequate. I am not advocating scattering money to all corners of the country where much of it will be wasted. I think this is an occasion for applied research into the introduction of new technologies which needs to be directed and needs to be done on a large cooperative scale to get answers quickly.

Some diseases with a known genetic cause are not being diagnosed, in part because doctors are not aware of the possibilities, but also because the research laboratories have difficulty in coping with the demands implicit in mutation testing in a family, and then—and this is often the most difficult part—taking on the extension of the family and the identification of other individuals at risk.

3.2 I don't think so.

3.3 In general, I think it is reasonable for insurance companies (who already ask for family histories) to ask for the results of genetic tests which have already been done at the request of the individual. I do not think they should be able to require the test be done before considering someone for insurance.

3.4 Population screening for genetic disease is only appropriate when there is some simple acceptable and effective action to be taken on the information gained. The health service will have to take into account costs and benefits, and they will have to include among the costs the need to educate and counsel people about testing, at least in the early days. I do not see that there is anything different in principle about how this type of screening should be organised and regulated, compared with any other—for example mammography. It would probably be efficient and lead to fewer mistakes if genetic typing were concentrated in a few centres rather than in every regional genetics lab.

Regulation will be important, however. An immediate worry is that private companies might set up offering population screening for genes such as the recently discovered BRCA1 breast cancer gene. Without close regulation, this could be very harmful. The risks associated with the inheritance of such a gene in someone without a family history are not clear, nor is the action which would follow from a positive genetic test. Regulation has to ensure that genetic testing does not take place without approved arrangements for ensuring that subjects are adequately informed and understand what they are doing beforehand, and have access to treatment, counselling and support afterwards.

3.5 People should be protected from discrimination, except in a few very specific cases where their genotype makes them very unsuitable for some occupations. It seems to me that this is not in principle any different a problem from discrimination on grounds of colour or sex.

3.6 Here we are dealing with recessive conditions. I can imagine that an individual might get themselves screened for mutations in known recessive genes, and if any were found, ask a prospective sexual partner for information relevant to those genes. I would think it likely that some individuals will do this, for a few genes which are associated with diseases which cause severe suffering or continuing burden to the offspring. At the very least, this genetic information should allow the couple to seek genetic testing early in pregnancy with termination of pregnancy if appropriate. I would think this is likely to change both with future research, which may uncover more conditions for which some kind of preventive action can be taken if the condition is suspected beforehand, and it may also change with changing social attitudes to the use of genetic information.

4. Economic benefits

4.1 Although much of medical treatment is empirically based, it is likely that in the future the design of drugs or treatment (including prevention) will be increasingly based on knowledge of genetic predisposition and its mechanisms. In my own field of cancer, I would think this is likely to be particularly important from the point of view of prevention.

5. Research

5.1 Mapping and sequencing the human genome may provide important biological insights of its own. Apart from that, at a practical level I think the main advantage is that this type of work can efficiently be carried out on a factory scale by specialised labs, with facilities that are far beyond the reach of the ordinary biology or medical research lab. The genome information which will become available will make it very much quicker and easier for biology or medicine based labs to understand the mechanisms of disease. This applies not only to inherited disease, but to any disease in which altered gene function at the inherited or cellular level is involved. The advantage of mapping expressed genes is that it should be quicker and for the most part in terms of practical application it is the expressed genes, in a wide variety of tissues, which are of crucial interest. Genomic sequence surrounding genes of interest can fairly rapidly be acquired when it becomes relevant.

5.3 The environment undoubtedly influences the expression of genes. Other genes also influence the expression of genes—in other words the final result is dependent upon the total "hand" of genes which one is dealt, and the interaction of the environment with them.

5.5 I think the financial support for research in human genetics is inadequate, specifically in the area of understanding gene-gene and gene-environment interaction. It seems to me that although this is a difficult research area, in principle it is nevertheless tractable. It is in this area that we have the best hope of identifying genetic predisposition which is important in common diseases, and of identifying genetic predisposition which is important in common diseases, and of identifying the factors which modify the predisposition and which potentially can be manipulated.

Memorandum from Professor Adrian L Harris, ICRF Clinical Oncology Unit, The University of Oxford (HGC17) (1 December 1994)

I enclose some selected answers to the questions that you raise particularly from my personal experience.

SECTION 1

1.2 Because we have applied to carry out gene therapy research for treating cancer I would say that the current policies are adequate. Safety is a key issue and has been followed in a responsible manner, but in a manner that does not hold up the potential therapeutic benefits. However, as technology develops a new series of questions may be raised, particularly those outlined in question 1.5.

1.5 If germ line intervention is simply to correct a defect and the alternative is to carry out an abortion, I would have thought ethically it is far less of a problem to correct the defect than it is to kill the unborn child. I think it is important to define what germ line intervention means and at the simplest level a correction of a single genetic change to the normal should be allowed.

SECTION 2

2.1 From my experience with cancer patients the vast majority are aware that there is possibility of new treatment approaches from genetics and they are enthusiastic and interested in trying this. Although there is some worry about side effects, there is far greater worry about death from cancer.

2.3 Expectations of the benefits are not unreasonable based on the large amount of *in vitro* and animal work that has been carried out so far.

SECTION 4

4.1 There is a massive stimulus to research in drug development if the genetic basis of disease is understood. These are very apparent in cancer where the genetic changes in certain genes and as oncogenes have provided many new targets for drug development.

4.2 I personally would say there is no basic difference between gene therapy and conventional therapy, both are ways of modifying the body to therapeutic benefit. In cancer, this may often mean temporary expression of the gene in the tumour which would then be eliminated if the cancer was eliminated so there would be no permanent genetic change.

4.3 Patent protection and regulation is absolutely critical for commercial exploitation of research findings. Premature publication without appropriate patent protection may mean useful drugs never get developed and in the end the patient suffers.

4.4 Venture capital funding in the UK seems very poor compared to the USA and this is a major problem for trying to develop new therapies here.

SECTION 6

6.2 Evolution has changed in that in the past it was a long term process, but now that social organisation can produce massive changes in the environment and life expectancy, this is a much more important form of evolution. Once could say that societies that have the best life expectancy and lowest perinatal mortality are those that are evolving in the most favourable way. However the same societies that have optimised survival and quality of life have also made the most severe environmental changes which may effect future generations and also the background mutation rate as a result of depleting the ozone layer.

6.5 To some extent selective termination has already been carried out in India and China either before or after birth to try and have boys where population growth is limited. Upsetting the balance of the population is likely to have severe long term consequences in terms of structure of society. The selection of one or other gender seems to me a much more serious problem than the selection of people are likely to be healthy as a result of correction of genetic defects.

One could put the question in another way, why let someone grow up and suffer when it could be possible to correct the defect that causes a particular disease? We are already practised in treating ill people and try to help them survive longer with modern therapeutics and life expectancy has gone up markedly. Therefore to a large extent many of these questions have already been carried out without any thought as to the effect on evolution. The result has probably been a great increase in human happiness, reduction in suffering, reduction in perinatal mortality, maternal mortality and many horrible diseases relating to infection have been eliminated. Why should gene therapy be considered any different in attempting to improve life quality and expectancy that has already been carried out for the last century? It is likely that much more marginal improvements could be obtained anyway based on the natural death rate of cells in the body and I don't think anyone is yet suggesting that we have ways to produce immortality.

Memorandum from Eve C Johnstone, Department of Psychiatry, The University of Edinburgh (HGC18) (30 November 1994)

It should be noted that these comments essentially address issues raised under questions 1, 2 and 3 of the document *Human Genetics: Questions.*

We currently have a degree of knowledge about the way genes work which informs our decisions about the use and regulation of genetic information. The principal relevant facts, although simple, do not seem to be clear in some articles designed for the general public in the popular press. To me the essential features are:-
(a) The influences of both genetic and external factors are to varying degrees present in all human disorders. (b) Many genetic disorders are the direct consequence of mutations in single genes, although there are other types of genetic disorders including abnormalities of whole chromosome (as in Down's syndrome), interactions of multiple genes and external factors early in foetal development which are the cause of malformations present at birth, and other interactions later in life between multiple genes and external factors—this last combination of causative elements seems to be the basis of many common serious diseases.

At the present time useful findings generally concern disorders which are direct consequences of mutations in single genes, e.g., cystic fibrosis, Duchenne's muscular dystrophy, Huntington's disease. Several thousand single gene disorders have been described: most of them are rare, many result in serious illness and death in childhood, causing much distress to sufferers and their families. Conventional treatments for these conditions are often inadequate and sometimes burdensome. The prospect of gene therapy for individuals, particularly children, affected by these conditions is obviously attractive. Few members of the general public or others would dispute the desirability of such treatments, which would involve interventions in somatic cells of affected individuals.

It is often not appreciated in articles for the general public that there is a clear distinction to be made between somatic cells and germ-line cells, as far as genetic manipulation is concerned. Germ-line cells during the first few weeks after conception are put aside in the embryonic sex organs to provide ova and sperm. Genes carried by germ-line cells may be transmitted to offspring and successive generations. Somatic cells include all other cells of the body. Genes carried by somatic cells have their role in the life of the cells of the tissues and organs of the individual whom they endow. The alteration to the genes of somatic cells will affect only that individual. Therefore gene therapy carried out upon an individual affected by a condition resulting from a mutation in a single gene will affect that individual only, and there is no possibility of the effects of that intervention being transmitted to offspring and to successive generations.

At the present time the distinction has been made whereby somatic cell gene therapy will be able to be conducted under regulations essentially similar to those regulating all research involved in human subjects, although there is to be a new expert supervisory body which will work in conjunction with local research ethics committees. It has however been decided that germ-line therapy should not be attempted. A decision has therefore been taken that some research topics should be prohibited because they are intrinsically likely to lead to insuperable difficulties.

I think myself that the current policies with regard to ethical consequences of research in human genetics are adequate, in that research in human subjects is restricted to somatic cells, where really the issues raised are not centrally different from those involved in other forms of treatment which have been conducted to date. It has been my impression, however, both from speaking to relatives of patients who are affected by single gene disorders, and from speaking to the informed public in the form of medical students and post-graduate students,

that the distinction between somatic cell and germ-line interventions is not understood, and that people are fearful that genetic interventions which can be conducted at the present time would have effects on future generations and could be misused to adapt the characteristics of the human race, i.e., to make them taller, more intelligent, etc. It is my impression that the general public as represented by the groups above would have very grave doubts about any form of manipulation which could have the above effects, and that indeed such manipulations would not have the consent of the public at large. It is further my impression that there is anxiety even among persons such as post-graduate students that while only somatic cell manipulation is legal at present, and only single gene disorders have been addressed at present, it is only a matter of time before the possibilities of addressing disorders associated with multiple genes of small effect will become much greater, and that issues such as changing the intelligence of the population will become a realistic possibility, sooner than those anxious to reassure them about the ethical nature of genetic research care to suggest. It would be my impression that these are matters where widespread informed public discussion would be valuable.

Issues relating to consent may be important in relation even to somatic cell gene therapy and in relation to genetic screening. Many of the single gene disorders which are relevant to these methods affect children, and they are often also so severe that they affect the reasoning and judgment of sufferers, so that at any age they would not be in a position to understand the issues involved, and others might have to consent for them. The validity of proxy consent is not generally accepted. If there were any question about extending this to affect the germ-line cells of such people, their ability to consent on their own account would be in question, and of course the ability of generations as yet unborn to consent to anything that would affect them is non-existent.

As far as genetic screening is concerned, persons affected by a condition may not be able to consent to the transmission (or not) of information about that condition to their relatives, even though that information would be highly relevant for them. This issue is not new, it has been an established concern in relation, for example, to Huntington's chorea, for many years. Nonetheless, such issues should probably be discussed at the present time and it is worth recognising that the screening of kindred of affected persons for genetic disorders may have adverse effects upon relatives who are found to be affected by a condition which is not yet manifest in them but for which there is no treatment. Huntington's chorea is a long-standing example of this, and familial types of Alzheimer's disease are another example. It is not helpful to a person in youth or middle age to learn that they are likely to develop Alzheimer's disease before they die, for there is currently no treatment for this devastating condition. I have myself in the past had experience of a family with Huntington's chorea whereby the second of a pair of identical twins committed suicide when the diagnosis was established in his brother, as he realised that he would come to be affected in the way that he had seen his father and uncles affected.

While the benefits of recent major advances in human genetics are great and discoveries which have been made cannot and should not be undone, the possibility of detriment to some individuals has to be remembered, and steps taken to alleviate distress by any appropriate means.

In spite of the concerns which I have expressed, I would myself see it as a great advance if the disorders which are my main area of expertise, namely functional psychoses such as schizophrenia and manic-depressive psychosis, could benefit from greater genetic understanding. These conditions are not familial in every case, but there are some cases where this is clearly an issue. In spite of all of the problems referred to above, the unsatisfactory nature of the treatment for many cases of these crippling disorders is such that I think that possible areas of detriment would be outweighed by the widespread benefits which could result from genetic understanding.

Memorandum from The Royal College of Midwives—Welsh Board (HGC20) (5 December 1994)

General ethical regulatory

1.3 The College is of the opinion that the best insurance against potential abuse of genetic research is a well informed public. Society does have a right to declare an interest and opinion in the course of such research.

It would be a truism to say that most researchers would argue that their research is essential despite the moral problems it causes, and because of this some regulation and monitoring of such work is necessary. Research goals must be considered in the widest terms and regulation carried out by multi-disciplinary/cultural group.

As a caveat, it is alarming to note that in journals such as Human Gene Therapy, papers on ethical/moral issues are almost non-existent.

1.4 Inevitably genetic research first leads to discovery of genes that cause specific conditions/diseases before treatment is available, if treatment is ever available. Much research has resulted in this unenviable position where the development of a medical condition can be foreseen without the ability to treat it. Genetic knowledge

is not at present the prelude to curative measures although only time will tell if this situation will change. Either way it is inevitable that this knowledge will be used to "improve" the world. Indeed it could be said that the eradication of disease is the goal of the medical geneticist.

1.5 Even when germ-live intervention is technically possible it has the potential to affect the offspring of the person treated and their descendants, and as such needs to be considered well in advance of technical capability.

The College suggest that French-Anderson (1987)[1] has valid points to make when he says that germ live therapy should only be considered when:

— There has been success over time with somatic cell gene therapy.

— Animal studies suggesting reproducibility and reliability are available.

— There is public awareness and approval of procedure. (It affects society as a whole not just the individual as in somatic cell gene therapy).

Public awareness and education:

2.1 The setting up of regulatory bodies and the greater use of lay people on those bodies would begin to open up the debate to a wider audience and through that to better inform the general public. A good example of this is the Human Fertilisation and Embryology Authority. In going out for public consultation, their document on the use of fetal tissue and cadavers received huge media attention which generated useful and informative public debate. Clearly those individuals whose lives could be and are directly affected by gene therapy will require different information to those who do not.

2.2 Suspicion and anxiety is often caused by mis-information with the popular press often discussing what is at present scientifically impossible. However this does not preclude misuse of genetic information in the future.

2.3 For those people who do not come into direct contact with the genetic "service" unrealistic expectations are inevitable. It is those people whose lives could be affected by future technologies that require realistic and accurate information so that hopes are not dashed.

2.4 There is great danger that "socially unacceptable behaviour" could be explained away through genetics. Its root cause is multi-factoral and financially costly to attempt to put right. It is therefore always tempting to accept a simple uni-factoral cause and "treat" it with a uni-factoral solution.

Conclusion

The college is conscious that the increased use of antenatal screening procedures—a consequence of this research—has the potential to change the entire character of pregnancy from a normal life event to a medical episode, affecting women who are not "at risk".

Screening is just one way of reducing disability and the removal of people with genetic defects will not prevent suffering the world.

The college endorse the deliberations of The Kings Fund forum (1987)[2] in their consensus statement on screening for fetal and genetic abnormality which states:

"The primary prevention of environmentally determined congenital impairments and improving the facilities and attitudes of society to physically and mentally impaired people must be components of a comprehensive approach. The success of a screening programme should be judged not only by its affects on the prevalence of impairments at birth but by its total effect on the well-being of women and their families".

References

[1]French Anderson (1987). Human Gene Therapy in Ethics Reproduction and Genetic Control. Chadwick R (ed) Routledge, London.

[2]Kings Fund Forum (1987). Kings Fund forum Consensus statement: Screening for fetal and genetic abnormality. British Medical Journal. 1551–1553.

Memorandum from Marjorie McEwan Reid (HGC22) (4 December 1994)

The Questionnaire has been passed to me by The Religious Society of Friends (Quakers), Friends House, London.

For 16 years I worked as an Immunologist in Medical Research. I retired 10 years ago when genetic engineering was in its infancy, so I have some idea of the problems now facing the Scientists and those whose job it is to keep control of the results of new discoveries; also the disquiet felt by the non-scientific public. For some time a small group of Quakers, of which I am one, has been researching into what controls exist to keep the new discoveries within bounds. It is not possible to stop research but the uses of discoveries can be controlled by well designed legal restraints. It is in this area that I shall place my questions.

1.6 I think it is important to stress that the human genome is part of the human body and as such should not be bought and sold. I understand that the structure of the human gene is already being patented in the USA. I think it is essential that the UN takes a firm line on this and absolutely prohibits the patenting of the structure of genes, or of the genes themselves.

4.3 Patent protection gives a team of researchers time to exploit the results of their research. This seems fair in the development of drugs, but completely wrong if genes or part of them are the subject of a patent. For example, the gene for Muscular Dystrophy has been patented in USA. Consequently, anyone wishing to use that gene to develop a cure for the disease will have to pay royalties. This will hold back medical research and the treatment of disease.

4.4 This is an extension of the remarks in 4.3. There is danger that we have already lost out to the USA. However, it is important to press for control of Patent rights and other regulations on Genetically Modified Organisms in the EC so that all scientists in Europe would come under the same laws.

Memorandum by Professor M A Ferguson-Smith, FRS, Head of the Department of Pathology, University of Cambridge (HGC 23) (7 December 1994)

This memorandum responds to the six issues on Human Genetics raised by the Committee. The respondee is a medical geneticist, whose clinical duties include directorship of the East Anglian Genetics Service, Addenbrooke's NHS Trust, and whose research interests are in human genome studies. The latter involve research into the identification of the molecular defects in genetic diseases and the application of this research into clinical practice.

1. General ethical and regulatory

Enough is known about the potential hazards of genetic modification and the uses that genetic information may be put to make sensible decisions about regulating the use of genetic information (para 1.1). MRC and the Medical Charities have regulations which require hospital ethical committees to authorise all grants involving patients only after considering all ethical and social issues (para 1.2). The Nuffield Bioethics Committee is among several bodies which provides ethical advice at the national level. Society certainly has a duty to ensure that unacceptable types of research are prohibited on moral or other groups (para 1.3). For example, the genetic modification of microorganisms which make them more virulent and their release into the environment is prevented by the regulations set by the Advisory Committee on Genetic Manipulation of the Health and Safety Commission. Similarly, the genetic modification of human embryos that are to be implanted into the uterus is proscribed by the Embryology Act. It is a misconception that scientists in general and geneticists in particular are less concerned than others in society about the social consequences of their research. The evidence shows that scientists on the whole act responsibly in these matters. The public need have no fears about hidden agendas in genetics research (para 1.3).

In response to public concerns about ethical issues in human genetics, a substantial proportion (1-5 per cent) of the funds for human genome research in the UK, in the European Union and in the United States has been set aside for social, ethical and legal issues. On the other hand, a much too small a sum has so far been spent in the NHS to help in the transfer of the fruits of the genome project to clinical practice, specifically in the prevention of genetic disease by improved genetic diagnosis, genetic counselling and prenatal screening and diagnosis.

Germ line intervention on experimental animals (mostly mice) has been valuable in allowing the construction of animal models of human disease, in developing strategies for gene therapy and in determining the function of unknown genes. However, the results are not sufficiently predictable to permit germ line modification in humans in the foreseeable future and, quite correctly, scientists have imposed a moratorium on such human

experiments. In the far distant future, when much more is understood about conducting these experiments safely and with predictable results, it may be reasonable to return to this issue. For example, if it were possible by germ line therapy to confer inherited resistance to HIV infection, there might be a strong case for introducing that therapy. The alternation of "normal" characteristics, such as stature, obesity and intelligence by germ cell intervention raises a much more difficult dilemma about what level of perfection one hopes to attain. Fortunately the definition of perfection is also highly variable and one is on safer grounds with disease prevention. These discussions help to recall the claims of the early eugenicists who saw man's ability to control the evolution of his own species as the alternative to the diminishing role of natural selection (para 1.5).

There is a strong case for a UN declaration on the human genome (para, 1.6). It might state something to this effect "The International Project to map and produce a consensus sequence of the human genome is supported by the United Nations. We declare that this genetic information be made available without restriction to the peoples of all nations and for their benefit. We further declare that the genetic constitution of each person is confidential information. Breach of this information, including discrimination on genetic grounds, is an abuse of human rights".

2. Public awareness and education

Genetics is in general poorly taught in schools in the UK and as a result, schoolchildren are neither interested nor excited by it. There is much to be said in favour of changing the emphasis more towards a consideration of aspects which are of interest to the pupils themselves. These include the importance of genetics in disease, the genetic risks associated with reproduction and pregnancy, and how carriers of disease may be identified. Then at least pupils may be better prepared for the responsibilities of parenthood and have some understanding of how genetics may suddenly impact on their lives by, for example, the birth of a handicapped child (para 2.1).

There is some evidence that public awareness in genetics is growing. Coverage in the mass media is increasing. However, lack of understanding and suspicion about research in genetics is not assisted by the widespread viewing of films such as "Jurassic Park" and "First born" which is about a man-gorilla hybrid (para 2.2). On the other hand, there have been excellent documentaries on television on the human genome project and the prospects of gene therapy which, on the whole, have not proposed unreasonable expectations (para 2.3).

The evils of the racial hygiene policies of the Third Reich and the current "ethnic cleansing" (which is one of the worst forms of genetic discrimination) in former Yugoslavia, serve as striking examples of socially unacceptable behaviour. Less obvious examples, such as termination of pregnancy for gender selection (widely practised in Asia) and the prohibition by law of marriage between carriers of genetic disease (recently introduced in China) must be regarded as abuses of human rights. The question of termination of pregnancy for severe genetic disease or malformation in the fetus is rightly regarded as a matter for individual parental choice. The right decision for the parents may equally be continuation of pregnancy or termination, and society must be prepared to fully support either choice irrespective of the economic consequences for health care, education and welfare (para 2.4).

Personal characteristics of appearance, intellect and behaviour are the result of complex interactions between genetic constitution, environmental experience and a number of chance factors operating during embryonic development. The interplay of these various factors and their individual contribution to human variation require further research and questions should be addressed to these fundamental issues. A better understanding of homosexual behaviour could result from such research (para 2.5).

3. Genetic disease

Genetic medicine is largely preventive medicine, and its costs should be borne to a greater extent than at present by funds set aside for public health. This is because health purchasers are more concerned with making provision for ill people than for those who might be born later with some form of handicap. A hip replacement now is arguably of greater priority than giving genetic advice to a couple who may or may not have a risk of giving birth to a child with cystic fibrosis. The greater part of clinical genetics practice is making a correct diagnosis, identifying family members who have the condition or who risk passing it to their children, and giving advice about parental reproductive options. Another important aspect of genetics practice is genetic screening which has had a major impact on the reduction of serious birth defects such as Down's syndrome and spina bifida. Genetics identifies both those not at risk who can safely reproduce, and those others who may choose to have a healthy family after prenatal diagnosis. The effects are to allow parents to conceive who would otherwise not have risked pregnancy, and to allow them to choose to avoid affected offspring.

As a result of the human genome project, over 6,000 genes have been characterised and over 4,000 different genetic disorders are known. Most of these are very rare, but the number includes almost all of the most common single gene defects like cystic fibrosis, muscular dystrophy and Huntington's chorea. On the other hand, only a few of the genes which predispose to common chronic diseases such as diabetes, coronary artery disease and breast cancer are known. As research is being directed at these conditions new genes will be discovered with

increasing frequency. Research also leads to new and better diagnostic techniques for single gene defects. This research activity has led to a serious problem in technology transfer from the research laboratory to the genetics clinic. Genetics service providers' budgets are now directly dependent on contracts with purchasers who tend to be concerned with paying for services available in the past and cannot pay for developments which are happening at present and likely to be available in the future. As their budgets are fixed, the purchasers must take account of priorities and tend to regard benefits which come in future generations as less important than immediate benefits. Consequently, genetics services no longer have the ability to respond promptly to the clinical advances resulting from research and thus cannot provide their patients with the up-to-date treatment now available until new contracts have been agreed with purchasers.

In the past, budgets for genetic services were top sliced regionally and this provided sufficient flexibility to accommodate technology transfer. Development funds are now managed centrally and are being used for commissioned research. This is acceptable for major programmes into the development of prenatal screening and carrier detection in the population, but is not appropriate for maintaining service development in clinical laboratories. The Culyer Report suggests that a purchaser levy might be used to support intrinsic development in provider units. This would be a step in the right direction, but what is needed is a contribution from central NHS funds to genetics services in respect of their role in preventive medicine. As genetic services have been established on the basis of the old regional boundaries, their number are relatively constant and special central funding arrangements should not pose difficulty (para 3.1).

Information on an individual's genetic constitution must be regarded as confidential except in circumstances, such as law breaking, when innocent persons' rights may justifiably take precedence (para 3.3). In the case of employment and insurance it is important to distinguish between genetic tests which are diagnostic and genetic tests which are predictive. The employer and insurer is justified in knowing about a genetic disease from which a prospective employee or applicant for insurance is suffering and for which a firm diagnosis has been made. In the case of the employer, this may be relevant in terms of safety at work. Likewise, an insurer must be protected from fraud.

However, if a person has to declare every condition in which there is a probability that he may become affected in the future, this may seriously jeopardise his prospects of employment and insurance. The alternative open to him is to decline to have any predictive tests and this could have important consequences by delaying the identification of genetic risks to himself and to his extended family. The way out of this is to regard predictive testing as confidential and not to be declared, as it simply determines a likelihood that an individual may or may not develop disease sometime in the future. It should be noted that all of us will develop a fatal illness or accident in which genetic factors operate and may be identified in the future. To avoid fraud in insurance, an upper limit of insurance can be determined, above which a declaration about predictive tests is required. Under these circumstances the costs of the risk insured are spread evenly among all those who pay premiums, according to the benevolent philosophy of those who first established the friendly societies. Chance determines to which genetic disability each of us is liable and it seems appropriate that the costs should be shared (para 3.3).

Population screening for genetic disease is appropriate if the disease is serious, if the results provide useful information about treatment, or if the results allow parents informed choices about parenthood (para 3.4). The test should be sensitive and specific, i.e., not associated with high false-negative or false-positive results. Treatment should not only be possible but also available, and counselling and support should also be available to ensure informed consent and to avoid undue anxiety. Screening should be organised in special centres and on a scale which allows expertise to develop; there should be a critical mass of expert staff. There must be adequate quality assurance of tests and monitoring of results. As recommended by the Nuffield Council on Bioethics Report on the Ethical Issues of Genetic Screening, the Department of Health should urgently establish a central coordinating body to review genetic screening programmes and monitor their implementation and outcome. The results of screening should be confidential to the individuals concerned (para 3.3).

In theory, people should seek genetic information from sexual partners before the conception of children as this allows them the additional option of deciding not to conceive. In practice, this has certain disadvantages. First, it may cause anxiety and tension between a couple; this may lead to one partner withholding information from the other with associated guilt feelings. Secondly, people tend to put off genetic screening until pregnancy supervenes. This may be because they have insufficient knowledge about the condition for which screening is being offered. Screening in the antenatal clinic has the advantage that it is directed at the event in progress; that the mother can be screened when attending hospital anyway; and that it represents the most convenient and economic option. Once the level of understanding about antenatal screening has been raised sufficiently in the population, people can more readily appreciate the benefit of preconceptual screening.

4. Economic benefits

Knowledge of the genetic basis of a particular disease should more readily allow rational rather than empiric therapy (para 4.1).

There is no fundamental ethical or other difference between gene therapy and conventional therapy (para 4.2). In principle, gene therapy could well turn out to be more effective in that it targets therapy to the site of the problem, for example the treatment of a cancer by using a vector which is taken up by cancer cells and not by normal cells.

The commercial exploitation of genetic research has particular problems which require new international agreement. It is frequently stated that industry is seldom prepared to exploit new discoveries in genetics unless they can obtain an exclusive licence, which means that the discovery must be patentable. This is acceptable when the new discovery involves intellectual contributions resulting from new inventions or new processes. Many rightly hold that the decoding of a piece of genetic information does not constitute a new discovery or invention, but simply constitutes staking a claim on a piece of human genome which arguably belongs to each of us. Decoding a stretch of the genome is achieved by techniques widely available. The identification of the map position of a particular sequence is usually the culmination of work carried out in many laboratories world-wide, and not solely the discovery of the person who was first past the post in the final competition. For example, the breast cancer gene BRCA1, was correctly located by Dr Marie-Claire King's team on chromosome 17 several years ago and finally identified and characterised by Dr Mark Skolnick's team in Utah several weeks ago. Dr Skolnick was assisted by a company called Myriad, who invested much money in the team of 48 scientists who did the final work to clone the gene. The work would not have been possible without the collaboration of scientists in Washington and elsewhere and without the co-operation of many families with breast cancer. However, the patent application for exclusive rights of use of the breast cancer gene contained only the names of the Utah investigators. The patent may well be challenged. If it is successful it allows Myriad exclusive rights to the commercial development of diagnostic test kits and also to the development of therapeutic measures based on the gene sequence. There is considerable concern among medical geneticists that diagnostic tests for the breast susceptibility gene may be commercially available before the research is done to determine how the test should be used or what therapeutic benefits are available to those found to be carriers. There is a clear case for regulation until the necessary research is completed.

A comparatively small number of private companies have been established to identify and sequence expressed (active) genes from the human genome. These expressed genes constitute about 2 to 3 per cent of the human genome but comprise perhaps as many as 100,000 different genes. Progress has been fast and one company (Human Genome Sciences) in Rockville, Maryland, USA has so far developed a database containing over 365,000 partial sequences of genes estimated as being equivalent to about 160,000 genes; including some duplications. Perhaps 80 per cent of all human genes are partially represented in this database. Restricted access to this database is available to scientists and companies on the understanding that any sequence can only be commercially exploited under licence from Human Genome Sciences. The effect will be to restrict the number of useful sequences which are exploited for the benefit of society, for each sequence will be exploited at the cost of a licence and associated royalties. Other companies may be deterred from setting up their own sequencing programmes for developing similar databases.

If sequences of transcribed genes were not patentable and placed freely in the public domain, commercial enterprises would be able to choose suitable candidates for exploitation from any number of different genes. Thus, more opportunities would be developed, commercial exploitation of the genetic information would be more rapid, competition would be possible and costs to the consumer would be less. The scenario of Myriad charging what it likes for diagnostic test kits for breast cancer susceptibility screening is not one which clinical geneticists and their patients view with any enthusiasm. Costs to the NHS could be prohibitive.

Regulations for genetic containment in research seem to work satisfactorily in the UK, at least in Higher Education Institutes (para 4.4). There is evidence that UK based companies prefer to invest in North America rather than in Britain but it is not known if this is due to a more favourable regulatory regime abroad.

Commercial companies are not only interested in the human genome project because they see a market for medical diagnostics and therapies (para 4.5). They also see the genome as a source of sequence information which will allow them to synthesise protein products of genes with a variety of applications in biotechnology, nutrition, the drug industry, etc., etc.

5. Research

It is worthwhile to map and sequence the human genome because it leads to new knowledge in biology (para 5.1). It has already led to many important applications in medicine and biotechnology and the field is only in its infancy. In the short term, the greatest gains are to be made from identifying and sequencing the 2 to 3 per cent of the genome which consists of expressed genes. However, it is also very important to learn how genes are regulated, why they are packaged in a certain order in chromosomes and how and why chromosomes are spatially arranged in a particular relationship to one another in the cell nucleus. This type of knowledge will require complete sequence information of substantial parts of the genome.

One of the main outcomes of research in the human genome will be an appreciation of the function of many genes of unknown function. This will require detailed biochemical studies including studies of protein structure

including molecular modelling. Other methods for determining function include gene knock-out studies in experimental animals. The elucidation of function will be important in understanding embryonic development and the pathogenesis of congenital malformations. It will also assist in our understanding and treatment of cancers (para 5.2).

As indicated in the response to section 2, human characteristics are the result of complex interactions between genetic constitution, environmental experience and a number of chance factors operating during embryonic development. Environmental experience includes all types of external factors including nutrition, education, interactions with individuals and society, infection and immunity, accidents and cultural factors. It is far too simplistic to regard ourselves as only the products of our genes (para 5.3).

It is clearly conceivable that certain types of gene therapy may have unforseen and sometimes harmful effects, for example, by disturbing the balance of gene activity within the cell, or by disrupting the function of other genes. However, there are now a substantial number of cases where gene therapy has worked well and without untoward effects. This seems very promising but, nonetheless, we still do not know enough about the organisation of the human genome and more funding for research is required in this area.

6. Evolution

One of the by-products of human genome studies is the insight it gives to the study of the genomes of other species. The degree of conservation of gene sequence gives important clues about our own evolution and about our relationship to other species on the evolutionary tree. Among mammals there is great similarity in the order of genes along the chromosomes with relatively few changes in order which have been due to chromosomal rearrangements following divergence of species. The most extensive homology is found between man and the great apes. Protein sequence changes as well as small changes in gene sequence between primate species testify to the continuing divergence from our common ancestor and confirm palaeontological evidence (para 6.1).

It is difficult to discern continuing evolutionary change in humans, but it is likely that natural selection is less active in developed countries. The increased mobility of families and sub-populations around the world will tend to increase intermarriage and reduce ethnic variation in the future. Cataclysmal environmental events have been important in evolution in the past and will doubtless be so in the future. Their effects may be modified by advances in science. It can be safely said that selective fertilisation and selective termination will have no evolutionary impact.

Genetic manipulation of the germ line in experimental animals differs from natural variation in that it is not subject to natural selection (para 6.6). The mechanisms used in the laboratory for genetic manipulation are not those that occur in the natural environment.

Memorandum from Professor D G Harnden, Paterson Institute for Cancer Research, The University of Manchester (HGC25) (21 November 1994)

1. General, ethical and regulatory

1.1 We already know quite a lot about the way some genes work. It would not be surprising, however, if other mechanisms are still unknown. It is important in this context to recall that genes interact with other genes in the genome and also with environmental influences. It is not necessary or wise to wait till we have all the information about all genes before we consider the ethical implications of possible and proposed uses of information. Regulatory systems should be based on current knowledge and continually revised to take account of new knowledge. There is a danger that genetic information could be misused, even if early regulations are found to be imperfect, that would be better than allowing unfettered use of genetic information. It does suggest, however, that regulations should tend to be conservative, as in the early days of genetic manipulation.

1.2 The policies currently being pursued are reasonable as far as the laboratory science is concerned. The restriction on modifying the germline is appropriate at present. There is a problem over the patenting of human DNA sequences and there is a clear need to clarify the law in this area. This problem has both ethical and social dimensions. It is not right that specific companies should claim ownership of sections of the genome and thereby limit the use of these sequences or even exploit these sequences for profit. This would unquestionably require international agreement. There are also problems over the social consequences of the use of our genetic information. The availability of counselling services is, at present, totally inadequate to deal with the impending problems and Government should give urgent consideration to that matter.

1.3 Society certainly has a right to declare some research topics prohibited because of the possible moral problems. Obviously different societies and, in particular, different religions will have different views on that matter. I have no problems with the principle but, what is crucially important, is to decide upon the decision-making process. Most geneticists are acutely aware of these problems and they certainly must be involved in the decision-making process. How is it possible that logical decisions can be reached in the absence of those who have the most detailed knowledge of the processes involved? Equally, geneticists should not be alone in decision-making process. Lawyers, ethicists, social workers and others all have their part to play. Above all, the decision-making process must be open. Most scientists in the Western World do not have a hidden agenda. It is conceivable, however, that some members of society would seek to exploit our genetic knowledge for personal profit. It is also conceivable that some societies may be pursuing genetic objectives which the vast majority of people in the UK would find quite unacceptable.

1.4 One cannot say that "human genetics" *per se* will lead in any particular direction. Human geneticists, more than any other group in the population, will be aware of the genetic diversity of the population and will be aware of the need to base our understanding of human behaviour on sound scientific principles, whether these be derived from laboratory science or from behavioural science. These scientific bases will interact with other socio-economic factors in determining what actually happens. People will try to improve the world through genetic interventions and, within limits, they should. The problem is as in so many other fields, deciding where the dividing line, between what is acceptable and what is not acceptable, should be drawn. We already accept that if we can prevent children being born with Down's Syndrome or spina bifida, that is a benefit. Although there are those who argue that, as we eliminate these conditions, those who display them will come to be held in a lower regard than at present and we must be conscious that that does not happen. We must try to eliminate or ameliorate what a disease process is. I would draw the line at trying to alter normal characteristics; whether it be sex ratio, stature or intelligence. I appreciate that drawing a dividing line between these is not at all easy.

1.5 The main objection to germline intervention is that our knowledge at present is so limited we cannot assess what the impact would be. Any gene will interact with its genetic environment and while we may correct the problem which we have identified, it is possible that an inserted gene may have other less desirable effects. One can argue, however, that less desirable effects would rapidly be eliminated in an evolutionary sense. A dominant deleterious effect would rapidly be identified and eliminated; a recessive deleterious effect simply would not spread in the population. In the course of evolution there have been many changes, some gradual, some dramatic, which have led to the present state of the human genome. A few more will simply add to the evolutionary process.

The major danger of course, is not the evolutionary argument, it is the difficulty of saying what is desirable and what is not. The eugeneticists of the 1930s had a vision of trying to make the world in their own image. Were some sections of society to do that now, it would be just a wrong now as it was then.

1.6 This is an almost impossible question. Possible items could be:-

(i) The human genome should be freely available to all those involved in counselling families.

(ii) Genetic techniques may be used for the correcting of defects, but should not be used for altering what are normal characteristics.

(iii) Germline modification should not be permitted until we have further knowledge of its impact.

(iv) Decisions should, as far as possible, be agreed by international treaty, bearing in mind the differences between different societies.

(v) All matters relating to the use of the human genome should be subject to free and open discussion.

(vi) Steps should be taken to protect those for whom counselling or genetic intervention are not morally or ethically acceptable.

2. Public awareness and education

2.1 Interest in genetics is considerable in the general population but, knowledge of genetics is woefully lacking. Steps could and should be taken to improve the situation. This should start in schools in the teaching of genetics, within the biology curriculum which should also include aspects of human genetics. Discussion of ethics and morals equally have a place within the school curriculum. Turning now to more advanced levels,

there is an appalling lack of genetic education in the undergraduate curriculum for medical students; this should be part and parcel of their training. The principles of genetics are a separate subject but the genetic implications should be integrated with the teaching of other subjects. For other graduates there is a continuing need for an output of classical geneticists as well as molecular biologists. There is a dearth of population geneticists and those skilled in the more mathematical aspects of genetics.

Public education is also important and every opportunity should be taken to present both the factual aspects of genetics and the moral and ethical dilemmas on television, radio and in the press. Informed debate to de-mystisise the subject is the key to understanding.

2.2 Yes, I do believe there is anxiety and suspicion about research and genetics. It flows, as indicated above, from lack of information. An uniformed public is always willing to believe the worst, looking back at some of the mis-uses of science in the past. The anxiety is justified and can only be allayed by education and openness of discussion.

2.3 Yes, I do believe there are unreasonable expectations. These are often fostered by sensational reports in the press and on television. Bodies like the Royal Society and the British Association could do more to inform the public about realistic expectations. It will, however, take time and requires a sustained effort.

2.4 Again, yes there is a danger that genetics will be used as an excuse for socially unacceptable behaviour. It was demonstrated many years ago that there is an unusually high proportion of XYY males in institutions which housed behaviourally disturbed people. This suggests a tendency to criminality because of their abnormal genetic make-up. However, the vast majority of XYY males in the population are normal, acceptable members of society. Unacceptable behaviour will have many causes, both genetic and social and often a mixture of the two. Again, the line is difficult to draw. Genetic causes of mental subnormality could lead to a plea of diminished responsibility in court. My answer would be that it should be the mental subnormality which is the ameliorating factor and that the cause of that problem should not be a factor. I do not believe that genetics could be used to justify reductions in the social programmes. It would seem that politicians have reasons enough for doing that without turning to genetics.

2.5 Another impossible question. I think I can only reiterate the need for openness in all decision-making processes; the need for education and the need to bear in mind the diversity of the human population and the differences between the moral and ethical standards in different societies.

3. Genetic disease

3.1 The quality of routine medical service varies dramatically from one part of the country to another. It is undoubted that in some centres much is associated with research programmes. The continuity between the two is not well organised and there is an urgent need to assess the future demands on genetic services. It is certain that some diseases with a known genetic cause are not being diagnosed simply because the services are totally inadequate in some parts of the country. A secondary cause is the growing awareness of the genetic component in many diseases.

3.2 Specially for somatic cell gene therapy, the ethical questions are no different from other forms of treatment.

3.3 The results of current medical tests are only made available to employers, insurance companies and others with the express permission of the patient. This confidentiality is carefully safeguarded by general practitioners and hospital doctors. If the patient chooses, the information can be divulged. Similarly, information about the individual's genome should only be divulged with the authority of the patient. There is one possible area of difficulty here which is that the genome is shared with family members and divulging information about one person may well divulge information about others unwittingly, or even expressly, against their wishes. However, John Harris has argued that individuals do not have the right not to know, since we do not run our own genomes, we share them with our fellows, in particular, with our families. (There is a publication emanating from a meeting of the Cancer Family Study Group which considers all these issues? Biomarkers, Edited by Michael Steel 1993).

3.4 Screening for genetic diseases is appropriate when the tests are accurate and when some benefit can be derived by the people screened. There would be no point in screening unless adequate counselling is available and unless intervention is possible. Intervention, however, may not be just medical intervention. Social intervention to ameliorate harmful effects may be sufficient justification. Cost clearly is a factor and, as with most other medical procedures, one must balance benefit to the population as a whole against benefit the individual. Screening should be organised within the National Health Service. I personally object to private sector clinics, however, if such were approved, they would have to be licensed and regularly audited. The same, of course, would apply to NHS laboratories and counselling services. The details of the organisation would depend on the frequency of the disease. Some would have to be nationally organised, others regionally, while some tests could perhaps be done at family doctor level.

3.5 There are different degrees of discrimination. Institutionalised discrimination can be dealt with by legislation. However, much discrimination is at the personal level which cannot be dealt with by legislation. There, the only way to deal with it is again education. The more people know and understand, the less likely will be discrimination. There is reason for hope because of what we see in the greater acceptance of people with a variety of disabilities in our present society.

3.6 It would not be unreasonable to seek genetic information, for example, a known carrier of a cystic fibrosis gene in the future might reasonably wish to know whether a potential sexual partner is also a carrier. What they choose to do with that information, however, is their business but, that knowledge can prevent the birth of a first child with a recessive disorder and, at present, it is only the birth of the first child of the disorder which leads to the potential of protection against the second. Information of this kind is already used for genetic counselling, for example, for thalassaemia. I think it will be used, however, I don't think this is likely to have an impact except in a socio-behavioural sense.

4. Economic benefits

4.1 At present, the main assistance in the treatment of disease, is simply the knowledge that the disease has a genetic component which can lead to surveillance or early treatment. However, as we come to know more about the function of the genes which confer susceptibility to disease, there is absolutely no doubt that this will lead to new methods of treatment. Knowledge of the function of the CF gene gives a potential target for therapy. This might be by gene therapy but, it may also be by the development of specific drugs.

4.2 There certainly are differences in principle between gene therapy and conventional therapy. The latter seeks either to modify the behaviour of existing cells or, indeed, to destroy them, whereas the former seeks to replace the function or modify it in a permanent way. There are substantial differences also in practice. For example, enzymic treatment for Gaucher's disease requires to be repeated for a lifetime. Successful gene therapy could lead to the complete elimination of the disease in one treatment for a lifetime. I doubt if there will be much difference in development costs. It already is enormously expensive to develop a successful chemotherapeutic agent and I think it is likely to be the same for gene therapy. As indicated above, gene therapy has the potential for being more economical but, only if there can be successful targeting of stem cells and continued expression of the transgene. That still has not been achieved for any disease.

4.3 All these things crucially influence the commercial exploitation of research findings. We do not have sufficient technology transfer facilities; patent protection and regulation, as already indicated, is a shambles. The whole question of commercial exploitation of genome research is one which has to be clarified. I will again emphasise that I believe that direct use of the genome for family counselling should not be subject to patent protection. If a gene is used for the development of a specific therapeutic agent then that agent, obviously like any other therapeutic, could reasonably be protected by a patent.

4.4 I have little knowledge of regulatory regimes in other countries. There certainly is a danger that investment will be lost to other countries which have better venture capital funding. The explosion of genome-based companies in the United States it at present dramatic. These are finding partners in the large companies which can do the large scale scale-up. We are seriously lagging behind.

4.5 It is quite likely that there will be some cosmetic outcomes of human genome research and then we are on the tricky borderline between what is acceptable ethically and what is not. For example, a cure for baldness is a distinct possibility and I see no harm in that. But, enhancing stature, except for those who are clearly dwarfed, would not be acceptable.

Detailed knowledge of the human genome is also likely to lead to more rapid exploitation of the genomes of agriculturally-important plants and animals. At present, human genome research is well ahead but, undoubtedly, will have spin-offs for other species.

5. Research

5.1 It is worthwhile because of the perceived medical benefits which could accrue. There is also intrinsic scientific merit in understanding the nature of the genome and its function. The mapping of expressed genes is a good starting point because it is there that we are likely to encounter the most medically important genes. Sydney Brenner still talks of the rest of the genome as "junk". I am very far from convinced that that is so and, until we know more about the tertiary structure of the DNA, of its replication, and transcription, I don't think we can call the rest junk. Therefore, sequencing of the entire genome is of value.

5.2 The most important thing about the genome project is the huge investment of money. Any research project which has money thrown at it, is likely to progress faster. One can argue that this is not always wise but, at a time when there is a burgeoning of the role of genetic factors in human disease, it doesn't seem a bad

way to invest the money. One could almost say that because of the rapid discovery of disease susceptibility genes, this should be a top priority.

5.3 Virtually all human characteristics are determined by an interaction between environmental factors and the expression of genes. At the extreme end, some dominant characteristics such as, for example, polydactyl, may be almost entirely genetic, while getting knocked down by a bus may be largely environmental but, not necessarily so. I think one should have, as a working assumption, that all disease is an interaction between genetics and the environmental factors.

5.4 There is still much to learn about the organisation of coding information. We are on a rapid learning curve and it is conceivable that interventions could have unforseen effects. Studies on animal models would help to elucidate this.

5.5 In financing research in human genetics, one should not neglect important research in other fields. If the total pot is limited, I think human genetics has a reasonable share at the moment. I am all for increasing the size of the pot. One area where more money could be applied is in the delivery of the results of the research; that is definitely falling behind.

6. Evolution

6.1 It is not reasonable to expect evidence of continued evolution in the timescale that we can make direct observations. However, the examples of genetic drift and founder effects, clearly demonstrate that major genetic change on a population-wide scale is possible. Evolution will continue no matter what we do. We may, however, succeed in altering those factors which determine the selection process. After all, the only ultimate success is the success of one piece of DNA replicating itself more often than another.

6.2 Modern social organisation is likely to have some impact on evolutionary processes, but the timescales are such that I do not think we can possibly predict what the consequences would be.

6.3 Similarly, environmental change will alter the selective pressures applied to human populations and, therefore, will have evolutionary consequences. What these consequences will be, it is impossible to predict. The timescale is just too long.

6.4 Again, the pursuit of scientific knowledge may increase our understanding of human evolution and, in the sense that it enables people who would formerly have failed to reach reproductive age to survive to pass on their DNA to another generation, it will have an impact on human evolution but, what that impact will be will not be apparent for a very long time.

6.5 Selective fertilisation, if it permits genes to be passed on which would not otherwise have been passed on, will have an impact. Similarly, termination, if it prevents DNA sequences being passed on will have an impact. Our knowledge is so imperfect and the timescale so long that we cannot guess at the consequences.

6.6 Manipulation of the germline, if we ever do it, may not be all that different from some of the events that have occurred in our evolutionary past and perhaps even as a result of the action of transposable elements in our present state of evolution. However, it is very different from the slow change that one normally sees in the process of say the selection of particular breeds of domestic animals. It is more like the traumatic changes which can be wrought by the manipulation of domesticated plants where whole chromosomes, or whole sets of chromosomes, can be exchanged. The crude method of gene transfer which we presently employ simply deliver genes either as episomes, which is not natural in mammalian systems, or integrated into inappropriate locations within the genome. It may eventually become possible to place genes in exactly the right location in their correct regulatory environment. That presumably would be much less likely to have deleterious consequences.

6.7 If this is suggesting that clinical interventions are likely to replace sex, it seems to be a highly unlikely situation. The scale on which gene manipulation is likely to be practiced will be trivial compared with natural sexual reproduction. If the clinical intervention enables childless couples to have children, if it enables couples to avoid having mal-formed children, then I think it should be not only permitted but encouraged. I think human sexual drive will take care of the rest without us worrying too much about it. Huxley's brave new world is still a fiction and likely to remain so for a very long time.

Memorandum from Professor Kay E Davies, Institute of Molecular Medicine, Oxford (HGC26)
(6 December 1994)

1. General and ethical and legal issues

1.1 We do not need to know how genes work before we can make decisions about the regulation of the information. We already have sufficient knowledge about the potential of this information to make decisions on what regulation might be required. In addition, it is best to make such decisions before the science is able to deliver rather than after.

1.2 The current policies are certainly adequate although more needs to be spent on educating the layman and schoolchildren in a science that is likely to have a major effect on their lives.

1.3 I believe that society does have a right to control the use of scientific advances which on balance do not benefit society as a whole. Genetics are already aware of this and the Ethics Committee of HUGO (Human Genome Organisation) is dealing with this. Granting agencies are allocating a proportion of their budgets to this. I do not think they are pursuing agendas of which the public are unaware.

1.4 People could try and improve the world by genetic intervention. However, behavioral traits are caused by the interactions of several genes and the combination of genes which are important will very from individual to individual. I therefore think that this is unlikely. Eradicating a disease such as cystic fibrosis may become feasible and may be desirable.

1.5 Germ line intervention should not be completely banned. There may be circumstances where chronic diseases of childhood such as cystic fibrosis and spinal muscular atrophy would best be eradicated this way. There is an objection to doing this if it is not going to increase the quality of life of the individual or society as a whole.

1.6 UN declaration on the human genome should cover the issue of confidentiality of genetics information and the use of this technology for serious disease.

2. Public awareness and education

2.1 There is an awareness of genetics in all sectors but the level of understanding varies. The press have covered genetics quite extensively. Education programmes in schools should be introduced. In my experience of giving several lectures in the field, sixth formers have only grasped the eugenics aspects and are deeply suspicious of the science as a whole.

2.2 This fear and suspicion could be allayed to some extent by making the debate between Government and scientist as public as possible.

2.3 Overall, I do not think expectations are exaggerated. Timescales might be but then this field has always moved faster than predicted.

2.4 There is a danger that genetics will become an excuse. This is why we need a better understanding of how these genes affect behaviour. It is probably not ethical to give out information which is not in the interests of the individual and where nothing can be done. This is why current genetic screening is voluntary and confidential.

2.5 The modification of behaviour through the manipulation of genes is so far off that it would be better to concentrate on the major disorders such as diabetes, heart disease and asthma. Genes for schizophrenia would be acceptable to all as targets for modification if they are found. This would be of benefit to society and the individual.

3. Genetic disease

1. Most of the major single gene defects are being diagnosed routinely. The transition from research programme to service could be improved. Funding for pilot screening projects in polygenic disease will be important. Both the ethical and scientific issues need to be addressed in any such study.

2. No.

3. The information should remain confidential. It is different from any other test because it is predictive, in some cases in a definitive way. Thus results will affect an individual's ability to obtain insurance or it may affect the premium.

4. Population screening for a genetic disease should be considered if something useful can be done with the information. This may be treatment or advice on lifestyle. The availability of counselling is essential. All new

genetic tests need careful pilot studies that cover all aspects. This applies equally to gene therapy. The screening is best organised in a partnership between scientist, NHS managers and clinical geneticists.

5. Avoidance of discrimination is difficult but the risk factors will not be absolute determinants. People will probably need some protection against such events.

6. Screening could be done at school age, prior to marriage or at the time of conception. The timing will depend on the genetic disorder being screened for. Again individual choice will need to be protected. A good example of this is the fact that few Huntington's Disease potential carriers have opted for screening. If there was some treatment, then the situation would dramatically change.

4. Economic benefits

1. The knowledge of a disease gene allows more specifically targeting treatments to be devised. It may elucidate novel biochemical pathways. The recent identification of the obese mouse gene which conserved in man will almost certainly lead to novel insights into obesity.

2. There are few differences in gene therapy and conventional therapy. Perhaps in gene therapy the researcher might be involved in phase I trials which would require production facilities.

3. The patenting of genes is severely affecting the field and its exploitation.

4. There is definitely under-investment in the UK. Several young investigators have left the country to begin start-up companies in the USA.

5. Human genetic research is also having an impact on other genome research. The advances in technology will thus benefit agriculture and farming.

5. Research

1. It is worthwhile to sequence all the genome because although only 3 per cent encodes genes, the intervening DNA had important functions in regulation of the genes. Without prior knowledge of this, it is not sensible to neglect any part of the human genome unless it is obviously very repetitive and devoid of genes. It is of short term benefit to sequence genes first but ultimately the rest will be required.

2. With a complete map, the potential to analyse genome diversity and the populations is enormous. It is necessary to analyse multiple variable sites to do this.

3. This is impossible to answer but it is probably safe to say that most disease has a genetic component.

4. Very little is understood about the organisation of coding information in the genome and only the whole sequence will tell us this.

5. There needs to be more investment in human genetics if we are not going to be left behind. As the knowledge accumulates, we will need more investment in informatics for sequence analysis and for the testing of gene function.

6. Evolution

The study of genome evolution will allow us to understand why certain diseases are prevalent in certain areas. The data also support the notion that there are few differences between individuals of different racial groups than there are between individuals within a single race. Thus the study of genome evolution is not likely to increase racial tension.

The time scale of human evolution is obviously large and the eradication of gene mutations that no longer give selective advantage is beneficial. The study of the evolution of disease mutations helps understand the selection processes. Decisions on modifications to the germ line which are unlikely to have long term harmful effects can thus be carefully chosen.

Memorandum from Dr S Hodgson, Guy's Hospital (HGC30) (7 December 1994)

I would like to make a few points, from my standpoint as a senior lecturer in clinical genetics with a particular interest in cancer genetics. I think we are at a very important watershed in our understanding of genetics and the scientific and technological aspects of this are proceeding extremely fast. As we have seen in the past, this may exceed our ability to cope with the ethical and public health aspects of our rapidly increasing knowledge about genetics. I believe that in the UK clinical geneticists are very much aware of these problems and have their own professional forum in the Medical Genetics Society in which these issues are discussed and guidelines drawn up collaboratively for coping with these issues.

I think however that there may be serious problems:

(1) with the potential misuse of the new genetics by companies interested in making financial gain out of patenting genes, and

(2) the potential misunderstandings that may arise from biased publicity about genetic issues in the media.

To my mind these are the main areas where difficulties may be anticipated. I think it is unlikely in the present social and political climate in the UK that there would be widespread wilful misuse of genetic information, (although this may not apply elsewhere), but with the identification of genes that predispose to relatively minor characteristics such as homosexuality or obesity, individuals may request testing or even prenatal diagnosis for this type of genetic trait, and the ethical implications of this are of course huge. There are many factors which influence choices utilising genetic information, and these include the strength of the genetic predisposition, i.e., its penetrance—and its prevalence in the general population. To use the breast cancer susceptibility gene recently isolated—BRCA1—as an example, the media has publicised this in such a way that many people feel that it is a common cause of breast cancer and that screening in the population for mutations in the BRCA1 gene might become a possibility in the reasonably near future. There are a number of reasons why this is not so. Firstly mutations in the BRCA1 gene are rarely a cause of breast cancer and the majority of breast cancer is probably not due to such mutations. Secondly, different mutations in the gene may cause different degrees of predisposition to breast cancer, and some mutations may be more clinically significant than others. It could take many years to assess this. In addition it may be difficult to detect such mutations since they are very variable, and the technology for detecting them, together with the appropriate safeguards for accuracy of the laboratory testing, needs to be evaluated very carefully. It is quite likely that a false expectation could be developed in the population with regard to the possibility of general genetic screening for a susceptibility to breast cancer, which could be difficult to allay. The media may have limited understanding of the complexity of the situation and the way in which information is disseminated to the population is obviously a very important area which requires considerable thought and monitoring.

Screening for a genetic predisposition to particular common conditions, such as cancer, will also have implications for individuals tested with regard to insurance, employment, psychological impact and uptake of preventative measures in individuals found to be at high risk. Individuals found to be at low genetic risk may also suffer psychological sequelae. It is very important that such issues be evaluated carefully in small pilot studies before any widely based screening programmes are undertaken. Discrimination against people on the basis of their genetic endowment is quite possible, although discrimination already occurs on the visible effects of such an endowment, such as the colour of skin, height, sex and intelligence already. However many aspects of the genetic background of a person may never become apparent during their lives, particularly in the case of carrier status for autosomal recessive diseases, so discrimination based upon such a background alone could be very unrealistic. Issues of confidentiality with regard to the results of any genetic tests performed are thus of great importance and need to be considered with extreme care by a multi-disciplinary group of individuals, including non-geneticists, as a priority.

Finally, I think the economic factors involved in offering genetic tests will depend very much upon our ability to avoid financial exploitation through patenting of genes and widespread commercial involvement. I think this is a vital area in which control should be maximised. The potential benefits of genetic screening could be enormous but they need to be evaluated very carefully in a controlled way without confounding issues such as financial interests creating a bias in the way these issues are confronted.

Memorandum from Dr E Anionwu, Institute of Child Health, (HGC31) (8 December 1994)

2. PUBLIC AWARENESS AND EDUCATION

2.1 More steps should be made to ascertain what type of information the public wants, in what format and in what languages. The professionals should not assume that they know this already.

Opportunities for information and discussion about the relevance and dilemmas surrounding present and future knowledge concerning genetics should be available in:

schools—using the opportunities provided within the Science section of the National Curriculum.

primary health care settings—e.g., in general practice, antenatal clinics and family planning clinics.

the media—such a radio, television, newspapers and magazines.

All information should recognise and be sensitive to the diversity of cultures, beliefs, languages and levels of education and literacy within the different populations of this country.

The Nuffield Council on Bioethics report on Genetic Screening: Ethical Issues recommended that "A wide range of educational aids about genetic screening is required. We hope that the Department of Health will take the lead in addressing the different sections of the community, enlisting the media to help with the task".

3. Genetic disease

3.1 There needs to be clearer evidence that there is equity in respect to the resources allocated to both research and genetic services for various genetic conditions. Two examples of conditions that might be neglected are:

(1) the very rare genetic disorders and.

(2) Those primarily affecting black and minority ethnic groups, e.g., sickle cell disorders and thalassaemia.

3.4 Many of the questions raised here could be resolved with the acceptance of the recommendation in the Nuffield report (referred to above) that a central coordinating body be established to review genetic screening programmes and monitor their implementation and outcome. The Gene Therapy Advisory Committee is a possible model.

One area that gives rise to particular concern is the paucity of courses in genetic counselling in spite of the numerous reports that stress the need for informed consent and non—directive genetic counselling. There are only two short courses accredited by the English and Welsh National Nursing Boards, aimed mainly at nurses and midwives (at the Institute of Child Health, London and Department of Medical Genetics Cardiff) and one part-time 2 year degree course (Department of Clinical Genetics, Manchester University). In addition there are only two short, accredited courses on sickle cell disorders and thalassaemia (Haringey and Camberwell).

The huge educational needs that now exist of professional people such as doctors, nurses, midwives, health visitors, practice nurses, family planning staff, teachers and social workers is due to the inadequate training in genetic issues in their basic training. Equal attention should be paid to rectifying this within future courses.

As with the comments made in respect to the section on public education, training must embrace information about issues surrounding the offer of genetic information and screening relevant to diverse communities within this country. A multi—ethnic dimension such as this would incorporate the impact of culture, religion and perception of genetic burden in respect to decisions concerning various reproductive options. The need to be supportive and non-judgemental, regardless of the decision made, is seen by many to be a vital component of genetic counselling.

Memorandum from Dr R D Turner (HGC32) (9 December 1994)

Para 2.4 Is there a danger that genetics will be seen as an excuse for socially unacceptable behaviour?

A major concern is that certain families will be labelled (justifiably) as "Genetically disadvantaged".

The more diseases come to be recognised as having a genetic component, the more Insurance companies, Employers, and Lenders of money will wish to have access to an individual's Medical Family History. Once they know (for instance) that the incidence of breast cancer or mental disorder is much more frequent in a particular family then all members of that family will be under a shadow.

More and more family histories are being stored on NHS computer systems, and the Data Protection Act gives *every* data subject (ie every person named on the family tree) the right to have access to his or her record. All the Insurance company has to do is demand that the individual obtain his family history and give it to them before he or she can be given a policy (or a loan or a job or a place in University or whatever).

My own proposals would be:-

(1). To carry out a proper research project into the legal rights of individuals to keep their family histories secret. The countries to be covered by this enquiry should include:-

The UK

The EEC

The USA

Others?

The Law department in Hull University and I have put just such a proposal to a number of funding bodies (including the Nuffield Foundation) but so far without success.

(2). To consider as a matter of urgency how families with a recognised "Genetic disadvantage" should be compensated and/or socially protected from the public or private purse.

It is bad enough for any individual to know that certain members of their family have either cancer or genetically determined illness, and to know that they are at risk of developing the same disease, without every agency in the land denying them the ordinary opportunities of life as well.

The Americans with Disabilities Act, and other similar legislation, should be considered in this respect.

I have a large file of Press cuttings and other articles giving day to day examples of how genetic discrimination is already affecting individuals in this and other countries, together with statements from Life Insurance and other companies, and I would be pleased to give further evidence to the Science and Technology Committee if this would be useful.

Memorandum from Professor D J H Brock, The University of Edinburgh (HGC33) (6 December 1994)

1. General ethical and regulatory

Scientists are primarily driven by a spirit of enquiry; they want to know how the world works and how one makes sense of its extraordinary complexities. This is no less true in human genetics than in any other branch of the physical or biological sciences. Contrary to a widely held view, geneticists and other scientists do think quite deeply about the likely consequences of the investigations that they are pursuing and many are irritated by the accusations of irresponsibility that occasionally surface in the public media. I am unaware of any "hidden agendas" in the research goals of human genetics, although it is possible that the unravelling of the human genome will lead to a more deterministic view of human behaviour. I see it as a scientist's responsibility to explore and document the relevant contributions of nature and nurture, even if at times this may lead to uncomfortable conclusions. Medical Geneticists, who daily confront the tragedy of individuals and families with serious genetic disorders, will attempt to improve the lot of sufferers through genetic intervention. However, it should be clear that this is a form of "negative eugenics", the avoidance of physical and mental disability, illness and premature death, rather than "positive eugenics", where one seeks to alter the genetic make-up of future generations.

I believe that society does have a right to declare some research topics as prohibited. However, this should always be a last resort situation after careful consideration of the moral and practical issues. Too often the public response to new directions in genetic research has a knee-jerk quality and is an overhasty response to what is unfamiliar. Governments, in particular, should be extremely reluctant to proscribe research unless there is strong evidence that such research would be detrimental to the public good or is so fraught with uncertainties that there needs to be a decent period of inactivity. In my view, the proscription of research on early embryos is a difficult one to justify, given the likely balance of benefits versus disbenefits. On the other hand, research on human germline intervention, which could affect later generations in unknown ways, is an area where the government has a right to call a halt.

2. Public awareness and education

There is currently a great deal of interest in genetics amongst most informed members of the general public. At the same time there is very considerable ignorance of how science works and what it can achieve. Some of this can be put down to the poor quality of education in UK schools. A more important factor is probably the low esteem in which scientists are held, the perception that science is boring, and the fact that very few of our legislators have a science background. Newspaper articles, even in the quality press, present scientific research as a series of "breakthroughs", and this leads inevitably to unreasonable expectations of benefits that might accrue.

It is difficult to see how to break the cycle of poor science education, the low public profile of scientists and scientifically semi-literate legislators. One of the potential dangers raised in your questionnaire is whether advances in genetics might be seen as an excuse for socially unacceptable behaviour and for justifying reductions in social programmes of health, education and welfare. If this were to happen, and one hopes that it will not, it

would almost certainly be the result of misunderstanding and partial understanding of the biological facts involved. Somehow this cycle must be broken.

3. Genetic disease

3.1 The time-gap between discoveries made in research and their availability to be used as part of the medial service is smaller in genetics than in most other medical specialties. With the reorganisation of the Health Service, the traditional mechanisms for bringing promising new discoveries on-line have been eroded. Research laboratories often find themselves providing genetic services without an infrastructure to do this competently or well. Funding for developmental research, the taking of a new discovery and turning it to a robust medical service, is virtually non-existent. I believe that this area should be the responsibility of the Medical Research Council and that it is not fulfilling its role in this respect.

3.2 In theory, somatic gene cell therapy affects only the individual exposed to this new type of treatment. As such, I believe that there are no new ethical issues. Germline gene therapy is a different matter, and I would accept that for the time being research in this area should be proscribed.

3.3 Variation in an individual's genome is heritable, and mutations may be passed to successive generations. Furthermore, in X—linked receissives and cominantly inherited diseases, it is possible to acquire information about the probable genetic make-up of the lateral family. In this respect genetic testing is different from other types of non-genetic medical tests. It is my belief that such information should be confidential and that it should not be possible for employers or others to acquire this information or to demand genetic testing on those who are at risk. I should like to see some consideration given to the possibility of a genetic privacy act.

3.4 The phrase "population screening for genetic disease" means testing the general population, where there are no special indications of increased risk, for the presence of mutant genes. To date it has been used only on a small number of autosomal recessive disorders, such as sickle cell anaemia, B-thalassaemia, Tay-Sachs disease and cystic fibrosis. The most important factor determining the establishment of a population screening programme is the severity of the disorder and whether screening will allow people to avoid the risk of having affected children. Such programmes should always be voluntary and should be provided in context of appropriate counselling. Unfortunately, in the current climate of a cash-strapped Health Service, issues of cost are involved and anyone proposing such a programme would be expected to show that the averted costs of preventing the birth of a child with a severe disability are in some way comparable to the up-front costs of providing all other aspects of the service.

3.5 At present most genetic factors predisposing individuals to common multifactorial disorders confer comparatively low relative risks. It is therefore not practical to use genetic risk factors in realistic estimates of whether a person will be affected. This situation may change in the future, and if it does, I believe that people should be protected form discrimination by some form of genetic privacy act.

3.6 A considerable amount of experience has now been gained from screening programmes for autosomal recessive disorders. In general, people do not change their mating partners in order to reduce risk. They tend instead to proceed with reproduction but to ask that the pregnancy be monitored by prenatal diagnosis. I believe that this situation is likely to continue and that the idea of individuals seeking genetic information about their mating partners to be an improbable one.

4. Economic benefits

The major issue confronting the exploitation of genetic research is the patentability of genes. As an example, I would cite my own experience in genetic screening for cystic fibrosis. All the different cystic fibrosis mutations have been patented, and in principle one owes a royalty to the "inventors" for every test carried out. This becomes of particular significance in population screening, where a large proportion of the tests are negative, but where the royalty is none the less due. I would like to see legislation that proscribed the patenting of human genes.

5. Research

The nature of scientific research is enquiry and it is a consequence of human inquisitiveness. From a scientific standpoint, the answer to the question as to why it is worthwhile to map and sequence the human genome, is because it is there. It may be strategically sensible to concentrate initially on cloning and sequencing expressed genes, but in the long run I believe that we will proceed to sequencing the entire genome. Because it is research we do not know the answers as to what we will find; if we knew the answers we probably would not do the research. Similar questions might have been raised many years ago about nuclear physics and about the type of information that would have come out of a detailed exploration of atomic structures.

It is my view that the programme to sequence the human genome is one of the most important aspects of research in all branches of science. It will obviously have enormous consequences for a proper understanding of human disease, both genetic and non-genetic. While financial support for fundamental mapping and sequencing activities is probably adequate, I am concerned about the relative paucity of funds for developing important discoveries and for putting these into an appropriate Health Service background. This is a point on which I have already commented.

6. Evolution

There is no doubt that here is a degree of public unease about the possible effect of genetic intervention on the long term future of the human race. I think that this unease is misplaced, but it is too large and complex an issue to tackle in this document. May I refer members of the Committee to Professor Steve Jones' book "The language of the genes", which goes into the issue in considerable detail. I cite from a paragraph in his final chapter: "Human being have interfered quite quite unknowingly with their biological heritage since there first appeared on earth. Stone tools, agriculture and private property all have had an effect on society and in turn on evolution. Many people are concerned that the next phase of human history will be one in which genetics makes deliberate plans for the biological future. This expecting too much of science. Inadvertent change—evolution by mistake—is much more likely to be important than is any conscious attempt to modify biology"

Memorandum from The Methodist Church (HGC34) (8 December 1994)

(How we inform ourselves) about developments in genetics and their ethical implications:

- — Articles in the quality press; quality TV and radio programmes.
- — Literature (books, reports and journals), e.g., the Nuffield Report on Genetic Screening and the regular journals GenEthics, New Scientist, Nature, Scientific American, Journal of Medical Ethics.
- — Links with Methodists (and others) working in the field of genetics (which has included a small number of weekend consultations in recent years).
- — Information-sharing and awareness-raising in the Methodist Church at large.

Ethical dimensions

1. *How ethical issues are clarified*
   - (a) By responding to questions posed to the general public (e.g., the consultations mounted by the Human Fertilisation and Embryology Authority).
   - (b) Awareness-raising by conversations with those who are keeping themselves abreast of developments and are directly involved in research and application.
   - (c) Involvement in Church contributions to the formulation of public agreements on general ethical frameworks for genetic engineering, e.g., the European Convention on Bio-ethics.
   - (d) By listening to the concerns of church members and others who are seeking to find answers to the moral dilemmas they are facing.

2. *How do we proceed to form ethical judgements?*

By debate in groups and committees of varying sizes within the Methodist Church, and occasional debate in the Methodist Conference (the final authority in the Methodist Church in matters of theology and morality).

We bring to bear on the questions posed to us our Christian understandings of what constitutes human life and the sorts of attitudes, relationships and values which nourish human life.

3. *Illustrations* of our work up to the present (enclosed)[1]
   - — A report to the Methodist Conference (1990) on *The Status of the Unborn Human.*
   - — A report to the 1992 Methodist Conference: *The Ethics of Gene Therapy.*
   - — Submissions to HFEA on Sex Selection and Donated Ovarian Tissue.
   - — A DSR publication, "Human Genetic Engineering—Good or Evil?" by the Rev Dr David Hardy.

[1] Not printed.

4. *Key Moral and Ethical Issues*

(a) The fundamental question which is posed by the development of human genetic science is: What is a human being? One particular sharp form of this question is the following: When does human life begin? When a fetus reaches the point when it is capable of viable autonomous life, we believe it merits the full dignity and respect of a human being. In the period between conception and viability the embryo and fetus has human significance, and the degree of human significance increases as the fetus grows in the womb. We believe we should treat with appropriate respect all life which has human significance. This sets limits on information-gathering and interventions for which appropriate free and informed consent cannot be obtained. (For example, see paragraph (j) below.)

(b) We want to stress the full human dignity and rights of human beings who are born with a serious genetically-based disability or disease. Society must have enforceable rules which prevent such individuals becoming victims of discrimination in the public realm, and which ensures the allocation of appropriate facilities and resources to enable them to live with as much freedom and opportunity as possible. We therefore resist all applications of genetic interventions which imply that potentially disabled children or children likely to be born with a genetic disease are in any sense "second-rate", or a "burden on society" or unworthy of entry into the human family. In particular, abortion should not be *routinely* offered as a response to genetic information on an embryo of fetus which indicates a high probability of serious disability or disease.

(1) We record our concern about the reliability and accuracy of genetic testing in the foreseeable future. So long as the genetic information has limited accuracy, we should be extremely cautious about scientific claims to predict the likely levels of disease or disability after birth. In any case, society needs to debate what counts as "serious" disability or disease.

(2) The Methodist Church accepts that complex personal and social circumstances may sometimes lead to the recommendation of an abortion. But we believe that great care must always be taken to respect the human significance of the fetus.

(c) We resist the notion that genetic information, however complete (e.g., the human genome), is an exhaustive description of human existence or of an individual human being. Our Christian belief highlights the transcendent possibilities in each and every human being. Our capacities for relationships with other human beings, for communion with God, for imagination and for self-discovery, can never be fully explained in scientific or mechanistic terms. The conviction compels us to resist all attitudes which treat human beings as mere machines or "objects". or which make them means instead of ends. We affirm the myriad opportunities for growth as persons through moral, ascetic and spiritual encounters and resources. Human beings merit respect and reverence, as creations and gifts of God.

(d) The Christian tradition has always fostered a commitment to healing and wholeness of life for human beings. We therefore welcome the potential for therapeutic interventions arising from human genetics which are consonant with the respect which is always due to human beings. We believe that there are incalculable possibilities for good in the new knowledge and therapeutic implications which are becoming available; though there are also dangers.

(e) Enthusiasm for the good which can be achieved must be tempered by the costs involved. In a world of scarce resources, the potential health gain from the large sums which are needed for research and treatment in genetics must be assessed against the significant health gain we know is possible, among the poor in this country and especially in the third world, from improvements in public health and from the promotion of relatively simple and cost-effective medical procedures.

(f) Therapeutic interventions which are consistent with human dignity and respect require the free and informed consent of patients. Systems should be set in place which provide counselling relating to medical procedures and likely outcomes which are independent of medical personnel involved in research and treatment. One special case causes us concern: germ line therapy. Even if it could be proved to be safe, we would be entering uncharted moral ground when a person is making decisions which will affect future generations who clearly have no say in what is being done.

(g) We recognise that there is a thin boundary between therapeutic interventions on the one hand, and on the other hand, reverence for the "givenness" of human life (in all its variety). Thus, there are occasions when it is unclear whether respect for the humanity of people who appear to be outside the normal, conventional or acceptable range of variations means accepting them as they are or "treating" them for sickness or disability. (People with severe mental disabilities or learning difficulties are particularly vulnerable here). Where do the "natural" limits of human life begin and end? We need systems whereby the public can scrutinise developments in this area (e.g., on what grounds shall we as a society permit post-menopausal women to conceive?)

(h) There is another thin boundary, at the opposite end of the spectrum, between therapeutic interventions and the satisfaction of human aspirations. Society may sometimes be tempted to encourage genetic interventions which purport to be designed to eliminate or "improve" what is considered to be outside the normal, conventional or acceptable range of variation—but which are in reality merely a pandering to personal preferences (e.g., eye colour, height or the selection of gender) or cultural prejudices. The development of genetic science, we believe, will increase the potential for harm if society succumbs

to any form of eugenics. This we absolutely resist. "Designer" human beings, or cloning, should be firmly prohibited by law. We must set our wills against the notion that if we *can* do something, we *must* do it.

(i) With the power to transfer genes from one species to another, a whole new set of questions arises, which will need careful attention and due caution. Should we, e.g., resist changes to the genome of other mammals so that they more closely mimic the human genome? Although work of this kind might bring some benefits—e.g., in the treatment of disease—it could be a very dangerous area to move into. Similarly, the introduction of genes from other species into humans should not be contemplated without a most serious and careful consideration: could we foresee the consequences clearly enough ever to justify the risk involved?

(j) Consonant with our view of the high dignity of human beings, who individually and collectively are made in the image of God, we:

(i) Resist the sale of human genetic tissue, and payments for the provision of genetic resources towards therapy and research.

(ii) Believe that detailed genetic information about identifiable individuals must be kept *strictly confidential*. In particular such information must not be revealed to potential employers or to life insurance companies, without the individual's consent.

(iii) Believe that research on human beings must normally be carried out only with the free and informed consent of those who are to be the objects of research (see (f) above); and that research on products of conception, which are to be discarded afterwards, should continue to be strictly limited to the fourteen days after conception. Any kinds of human-based research which are regarded as acceptable without consent (which may include some research based on medical records) need to be clearly defined.

(iv) Believe that it is unacceptable to create pre-embryos by IVF in order to experiment on them.

(v) Object to the patenting of information relating to the human genome.

5. *Advances in genetic knowledge and the responsibility of society*

The Methodist Church wants to encourage informed debate in society at large on the ethical and moral issues raised by developments in human genetics. We hope that the Science and Technology Committee's report will highlight this theme. We also wish to underline the responsibility of Parliament and of the general public to undertake periodic reviews of the legislation and ethical codes governing human genetics. New knowledge and new applications of technology will suggest new questions, which in turn will require the revision of existing regulations and codes.

Memorandum from Alex Crawford, Editor, Laboratory News (HGC37) (8 December 1994)

1. General ethical and regulatory

1.1 *"What do we need to know about the way genes work in order to make decisions about the use or regulation of genetic information? Are we likely to obtain that information?"*

1.1.1 If we consider the definition of a gene to be "a unit of hereditary material that forms a discrete part of the chromosome encoding information in the form of a DNA sequence", then we do not need to know precisely how it works in order to make decisions about the use or regulation of genetic information, although such knowledge would help us to understand better the potential uses and abuses. There is a parallel with HIV test information, whereby we do not need to know the details of how a particular HIV test works in order to make decisions about the use or regulation of HIV test information.

1.1.2 There are some situations in which individuals should be entitled to receive genetic information. For example, where it might be a necessary precursor to:

— A decision about having children who might otherwise be born with genetic defects;

— A decision about medical treatment; or,

— Counselling—to accept the consequences of a genetic defect.

1.1.3 However, before anyone is tested, it should be clear what the purpose of the test is, their permission should be sought, and they should be informed of the outcome, and guaranteed appropriate counselling. This will require regulation.

1.1.4 There are other situations where genetic information should not be made available. For example, insurance companies should not be allowed to require genetic testing as a condition of granting insurance cover. This will also require regulation.

1.2 *"Are the current policies being pursued by the MRC and other research funding bodies with regard to ethical and social consequences of research in human genetics adequate?"*

1.2.1 At the policy level in the MRC and the BBSRC, for example, there is clearly an appreciation that there may be ethical and social consequences associated with research in human genetics. This is evidenced by the decision of the MRC to set up a Gene Therapy Data Monitoring Committee and to fund a single comprehensive national study of the psychosocial implications of gene therapy.[1] Also, the BBSRC has explored the possibility of using "consensus conferences" as a sounding board to investigate public opinion about such issues.[2]

1.2.2 However, it was only in last year's White Paper *Realising Our Potential*[3] that these Research Councils had public understanding of science incorporated into their mission, and they are still exploring how best to fulfil that role and what resources to allocate to it. They are perhaps hampered by the fact that their members and their staff are appointed primarily for their expertise in their areas of research and its application, rather than in the ethical and social consequences of that research. However, they have very talented communicators in their (small) public relations departments, which could be even more effective if they had more resources, particularly if they were directed at popular communications, such as TV, radio, film, and consumer magazines.

1.2.3 However, an important question is how such appreciation at the policy level is taken up in practice by the scientists funded by the MRC, the BBSRC and other research funding bodies. Generally, scientists' appreciation of such consequences of their work is left to their own sense of responsibility. In their day-to-day work in the laboratory, these consequences may not be given a second thought, as they strive to advance their work and keep up with the very rapid pace of developments in the field. Thus, when questioned, individual scientists will frequently disclaim any responsibility for wider issues on the basis that they are only scientists in the laboratory trying to do a good job, and it is up to their management and the Government to take care of the wider issues. Indeed, it is almost part of the culture in laboratories to refuse to be concerned with anything other than the task in hand—the techniques and the science needed to advance a project.

1.2.4 To redress this gap between policy and practice, there may need to be regulations imposing on the MRC and other research funding bodies an obligation to ensure that the managers of the programmes they fund in the field of human genetics draw up and implement action plans, which include training of the individual scientists in dealing with the ethical and social consequences of their research.

1.2.5 With this background, the question also arises as to whether society at large, as represented by Parliament, can delegate policies on the ethical and social consequences of research in human genetics to the MRC and other research funding bodies. Clearly, this cannot be the case. However, the MRC and other research funding bodies will equally clearly have a significant role to play in getting the scientists to internalise any obligations that UNESCO may lay down in the proposed Declaration of the Protection of the Human Genome. This approach may best be managed by a joint MRC/BBSRC/ESRC Commission accountable to Parliament via the Chancellor of the Duchy of Lancaster.

1.3 *"Has society a right to declare that some research topics should be prohibited because they are intrinsically likely to lead to insuperable moral problems? Should geneticists think more widely than their immediate research goals and their likely consequences or should they leave that to others? Are they pursuing hidden agendas of which the public is unaware?"*

1.3.1 No-one would advocate that scientists should be allowed to undertake research that would definitely lead to insuperable moral problems. However, if the research would not "definitely" lead to such problems but be "likely" to do so, the question then arises as to whether safeguards could be built in to avoid that likelihood. This is akin to work on radiation, where research does not lead to damage to the people or the environment unless safeguards are not in place to prevent exposure. It would be up to society, as represented by Parliament, to introduce safeguards for those areas of research which are intrinsically likely to lead to insuperable moral problems to ensure that the likelihood is not realised in practice.

2. Public awareness and education

2.1 *"What is the extent of knowledge of and interest in genetics among different sectors of the public? Should steps be taken to improve this and, if so, what form should they take?"*

2.1.1 Because genetics is of fundamental importance to everyone's health, there is inevitably great interest among the public. This is reflected in the extensive reporting in the media of the latest advances in research. However, there are several difficulties relating to this intense interest:

— As genetics is a most rapidly advancing field of research, on which governments and industry around

the world are spending hundreds of millions of pounds, it is very difficult for even well-informed scientists to keep pace with developments.

— As genetics is a relatively young field of research, the vast majority of the population have no formal education in it, so it is difficult for them to maintain a sense of proportion about the media's coverage, as they have no framework to which to relate that coverage; and.

— So much of the coverage is in terms of "breakthroughs", for example, in identifying genes associated with particular diseases or conditions. Journalists often feel forced to adopt this kind of approach because they are competing to capture their news editor's attention. As a result, a news item may only mention the long delay before treatment might be available as a result of the "breakthrough" right at the end of the item, if at all. In this way, the public is encouraged to have unrealistic expectations about what might be practicable, so creating a demand which cannot possibly be satisfied.

2.1.2 To redress this situation, the MRC/BBSRC/HEA could be funded to provide an appropriate programme in the public understanding of genetics. This could be an extension of the approach whereby the MRC has arranged to provide copies of its award-winning quarterly magazine, *MRC news*, to all doctors' surgeries.

2.1.3 Hands-on science centres and exhibitions could also play a role. For example, the MRC had a "Genes are Us" theme on a stand at the Motor Show this year. Also, I am currently involved in preparing a bid for submission to the Millennium Fund for a National Science Centre, themes of which (Health and Biotechnology) would include features on human genetics (See Appendix 1). The National Science Centre would also provide the setting for public lectures, displays, films, and demonstrations featuring topics in human genetics.

2.2 *"Is there a general anxiety and suspicion about research in genetics? Is it justified or should it be allayed, and, if so, how?"*

2.2.1 In the UK, there is no general anxiety about research in genetics, in comparison with, say, Germany, where pressure groups are very active in opposing the involvement of German scientists in such research. This opposition derives from concern about the role of some German scientists during the Nazi regime in providing support for racist and elitist programmes. Since UK scientists have never been associated with supporting such a regime, the public in the UK has not had the same historical cause for general anxiety and suspicion about research in genetics.

2.2.2 However, science fiction films, such as *Jurassic Park*, have enjoyed an enormous public success, and have raised public awareness about issues relating to genetic engineering. There is a need to counter the negative image that such films accord research scientists by encouraging geneticists to be involved in explaining their work and its significance to the public and in accepting their accountability to the public, as represented by Parliament.

2.3 *"Are there unreasonable expectations of the benefits that might come from genetics? If so, how should these be tempered?"*

2.3.1 See 2.1.1–2.1.3 above.

2.4 *"Is there a danger that genetics will be seen as an excuse for socially unacceptable behaviour? Could it be used to justify reductions in social programmes of health, eduction and welfare?"*

2.4.1 As knowledge grows about the role of genes in socially unacceptable behaviour, some people may seek to excuse behaviour on the basis that it is really beyond the individual's control. However, for particular types of socially unacceptable behaviour, those displaying it may be required to take genetic tests to determine whether it is associated with a genetic defect. If such a genetic defect is established, then, as long as the principles set out in 1.1.2 and 1.1.3 above are followed, it may be possible to modify the behaviour. If that is unsuccessful, it may be necessary for society to exercise direct control over the individual affected.

2.4.2 It is possible to envisage a situation where social programmes of health, education and welfare might have to be withdrawn from an individual showing socially unacceptable behaviour on the basis that they were ineffective because they could not address the source if that was shown to be genetic. However, those withdrawing the programmes should be obliged to provide an alternative, effective solution, as far as is practicable, along the lines set out in 2.4.1 above. The principle should be that, once born into this world, no human being, whatever their genetic make up, should be abandoned and left without support.

2.5 *"What are the right questions on the bearing of genetics on human behaviour, ethics and belief?"*

2.5.1 In an increasingly pluralistic society, it is difficult to see how there can be any "right" questions on the bearing of genetics on human behaviour, ethics and belief. In a pluralistic democracy, everyone should have the freedom to raise the questions that concern them as individuals, members of families, believers in a religion, or participants in a social group. Unless society is open and responsive to all such questions, there is a danger that particular individuals, sects or groups will feel persecuted or become isolated, and that can lead to breakdown in the tolerance on which the functioning of a democratic society depends.

3. REFERENCES

1. *MRC Annual Report April 1993—March 1994* (MRC, November 1994) page 8.

2. *UK National Consensus Conference on Plant Biotechnology, 2–4 November 1994* (BBSRC, December 1994).

3. *Realising our potential: a strategy for Science, Engineering and Technology* (HMSO, Cm 2250) May 1993.

Memorandum from The Free Church Federal Council and the National Free Church Women's Council (HGC38) (7 December 1994)

INTRODUCTION

This Response has been drawn up in consultation with individual Free Church people who have some medical/biological expertise.

As a background to considering this matter, we suggest that the four "prima facie" principles of medical ethics—together with their scope of application—must be borne in mind, viz: non-maleficence, beneficence (taken together—the net benefit of good over harm), autonomy and justice. The matter of scope of application is particularly relevant when considering genetic screening.

From the Christian standpoint, we urge the need to consider respect for human life—and care and compassion for the under-privileged, whether this is due to poverty, age, handicap or genetic make-up.

As Christians we must be guided by a desire to use God-given scientific endeavour and discoveries for the betterment of humankind as a whole; commercial gain or personal aggrandisement and ambition must not be the prime motivation for such work. At the forefront of our considerations must be whether the lot of the whole of humankind will be bettered as the result of scientific research into human genetics or whether the improvement of the condition of some individuals will be made at the cost of the condition of others—e.g., by diverting scarce resources of time, personnel or money away from less exciting work in, say, hygiene and public health and nutrition.

1. GENERAL ETHICAL AND REGULATORY

1.1 There is a need to know whether the gene is dominant or recessive, whether one or more genes are involved and whether or not an environmental factor also needs to be present. This knowledge is already available for some genes and our respondents expect that further knowledge—as it becomes available—will be disseminated.

1.2 We cannot answer this question.

1.3 We believe that society has such a right. Geneticists should consider consequences in conjunction with medical ethicists and others.

1.4 Research into human genetics does not, of itself, lead to determinism—though some try to apply it in that way. There are many more influences on human behaviour than simply the genetic ones e.g., environmental factors e.g., some factor which is specifically human (God-given), for instance the ability of some individuals to overcome very severe disabilities, even in the most adverse of circumstances.

Any suggestion of eugenics must be avoided.

1.5 There is a need here to look at the four principles of medical ethics, i.e., the balance of good over harm. In the case of germ line intervention this balance is not known and—except by allowing germ line intervention—cannot be known, i.e., a "Catch 22" situation. The generations to be affected are denied autonomy and justice remains a question mark. The balance, therefore, seems to be not to allow germ line intervention.

1.6 We believe that patenting of any part of the human genome must be forbidden.

Regulation

We feel that the Government should establish an overall strategy for research into human genetics: this should be done fairly quickly, drawing on expert medical and scientific advice, with input from sociologists,

philosophers, theologians and other interested and competent parties. We also believe that a controlling body to oversee human genetic research should be set up with a brief comparable to that of the body concerned with research into human embryos and "in vitro" fertilisation.

2. Public awareness and education

2.1 There is a growing interest and seeking of knowledge amongst those who, in general, take an interest in contemporary issues in the world around them.

An introduction, at least, to genetics should be part of the Science curriculum in schools and knowledge of the subject is vitally important before genetic screening—whether this is done on an individual basis (where there is a strong family history of a defect) or as partial population screening (e.g., in ante-natal clinics).

2.2 We feel that there is general anxiety and suspicion about genetic research amongst those who have some knowledge but are not experts. This is to some extent justified—available knowledge is very limited and we are entering uncharted waters; fears may best be allayed by a suitable regulatory framework.

2.3 We feel that press reporting has led to unreasonable expectations of the benefits of genetic research; it would be best if these were tempered.

2.4 There is a danger that genetics may be seen as an excuse for socially unacceptable behaviour, as sometimes are other factors such as poor environment. Such factors do have an effect on behaviour, but we believe that ultimately people remain responsible for their own actions.

We are opposed to genetics being used to justify reductions in social programmes of health, education and welfare.

2.5 This question was not understood by those we consulted!

3. Genetic disease

3.1 With regard to the first part of the question—inevitably, there is overlap between diagnosis conducted in routine medical services and in research. We can offer no knowledge about the organisation of continuity between the two areas.

Our answer to the last part of the question is "yes" as:

(a) More than one gene can cause a disease and not all are yet mapped.

(b) Screening, at present, is either individual (where there is a known genetic factor, e.g., Huntingdon's chorea) or partial population e.g., in most areas, women over the age of 35 are screened for Down's Syndrome as, percentage-wise, this condition is more common in older women; however, because of the greater number of pregnancies in women under 35 there are actually more babies with this handicap born to these younger women—though, at present, it is not considered cost/effort effective to screen them.

3.2 We do not believe so.

3.3 Yes—information should be confidential; the result of *all* medical tests are confidential and genetic testing should not be treated any differently.

We are concerned that people should not be disadvantaged in seeking employment or in obtaining insurance because of genetic testing. Hence, we would stress the need for confidentiality.

3.4 Cost-effectiveness, inevitably, is part of the equation. See also below "General comment" for further remarks relating to this question.

3.5 In answer to the first part of the question—by confidentiality and to the second part, our answer is "yes"—unless they are a danger to others.

3.6 We do not feel that people should, at present, seek or rely on genetic information about their partner before conceiving children. We recognise that this may change with future research, especially where serious illness or defect is involved.

General comment

We see a major problem in this area, where there are uncertainties with respect to side-effects, both medical and social. Counselling will be essential for those seeking "treatment" or whose genetic pre-dispositions (e.g., for Alzheimer's disease) becomes known.

The side-effects issue assumes particular importance with respect to transgenic individuals (wherein genes are implanted in the host's genome—e.g., the gene to synthesise insulin in diabetic patients).

4. Economic benefits

There is not the competence available to comment on this Section.

5. Research

5.3 This is variable—see *1.4* above and, again, there is not the competence available to comment on the rest of this Section.

6. Evolution

There is not the competence available to comment on this Section.

Concluding remarks

Despite the complexities of the primary sources in this field, the current state of human genetic research is still in an early state of development and an enormous amount is unknown; until our knowledge is wider, the uses to which it can be put for the alleviation of human suffering will be somewhat limited. We believe that it might be better, at present, to devote far more resources to understanding the genetics of micro-organisms, plants and animals—this would ultimately provide a better position to target areas for research and exploitation pertaining to humans. When that time comes, there will be a need to balance the considerations for the alleviation of suffering against a tendency to undertake narrowly-directed research based on curiosity rather than genuine altruism.

Memorandum from Pfizer plc (HGC41) (8 December 1994)

1. *What assistance in the treatment of disease or the design of drugs is given by knowledge of the genes associated with a particular disease?*

Current drug therapies are, in the main, based upon relief of symptoms associated with a particular disease. For example, H2 antagonists treat the symptom of hyper-acidity associated with gastric ulceration by interfering with the acid secretion mechanisms operating in the human stomach. Similarly, many other very successful drugs, such as ACE inhibitors in blood pressure regulation, HMB-CoA reductase inhibitors in hyperlipidemia and cyclo-oxygenase inhibitors in inflammation, are targeted at specific biochemical mechanisms which are *associated* with disease states. Although these drugs exploit our growing understanding of the biochemical basis of the disease, many have been discovered entirely serendipitously.

In contrast to this biochemically-based and somewhat serendipitous drug discovery route, companies are now turning to human genetics to provide a mechanistic understanding of human disease. Our knowledge of human genetics is growing exponentially, based primarily on our ability to sequence the key pieces of DNA corresponding to disease genes, and our ability to place them on the human genome map. Access to a complete map of the human genome will greatly facilitate the identification of those genes involved in inherited disease, and will provide new insights into the biological mechanisms underlying disease. For the first time, it will be possible to predict, both in specific families but also in the population as a whole, which individuals are at risk for developing disabling diseases such as Alzheimer's, stroke, high blood pressure, asthma, hopefully leading to better quality health-care, and potentially also to more efficacious therapy.

The two approaches to disease mechanisms, biochemical and genetic, converge. It will soon be possible to look at a complicated patient population, suffering from say asthma, and identify those members in which a *specific* biochemical mechanism of disease is implicated, and therefore predict which drug regimen to use. Alternatively, it may be possible to uncover completely novel and unexpected mechanisms underlying disease, which pharmaceutical companies can then exploit in their discovery programmes, either directly as drug targets or indirectly using their accumulated knowledge of the biology of the disease.

2. *Are there differences, in principle or in practice, between gene and conventional therapy? How might these affect development costs? How will this affect the actual cost of treatment?*

Gene therapy uses modified stretches of DNA as a way either to produce proteins in situ, or to interfere with the normal protein synthesis machinery of the body. These are fundamental biological mechanisms which have previously been largely inaccessible for therapy, the latter having centred mainly on the use of small molecular

weight chemical entities. Although the use of small molecule drug therapy can be highly advantageous in terms of both the cost of therapy and its predictability for the majority of patients, there are certain biological deficits which drugs cannot reverse. One example occurs in cystic fibrosis, where an in-built genetic deficit in a specific transporter molecule leads to disease and premature death. The use of gene therapy to correct this deficit, although at an early stage of development, holds promise for a radically different approach to during the disease. Gene therapy will offer a completely novel, alternative strategy through which to approach disease.

Development costs for conventional drugs are the single most expensive phase of the drug production cycle. Extensive Phase I and II studies to investigate human exposure and possible toxicological effects, together with efficacy trials, are often complex and time-consuming. The same safety considerations will inevitably apply to gene therapy, perhaps more so since our experience to date with such approaches has been so limited, and our initial studies need to be carefully designed and monitored. However, there is every reason to suppose that gene therapy in the long term will be as competitively priced as conventional drug therapy. The principle of a "gene in a bottle" is one which many companies are already embracing. The cost of treatment clearly reflects development and manufacturing costs: but there is every reason to suppose that both can be realistically minimised for genes just as much as small chemical entities.

3. *To what extent do factors such a technology transfer facilities, patent protection and regulation, influence the commercial exploitation of research findings?*

Patent protection and regulation is a key element in the commercial exploitation of research findings. The area of biotechnology patenting, ranging from patenting human genes themselves, to patenting their delivery systems, will be a key element in governing the take-up and development of these new genetic technologies. The Pharmaceutical Industry is unlikely to invest the substantial sums of money involved in complex development programmes if potential returns are immediately eroded by "generic" competition.

Technology transfer facilities, such as those established by the Medical Research Council in the UK, are important to early-stage research, and have been amply rewarded in other biotechnology areas such as humanised antibody therapy. Technology transfer can be very important in bringing new technology to the attention of large companies, but what is much more important is having an enlightened investment and regulatory environment. In this respect, the comparison between the US and Europe is highly unfavourable.

4. *How does the regulatory regime for genetic-based industry in the UK compare with that in other countries? Is there a danger that investment will be lost to other countries with different regulations or with better venture capital funding potential?*

The recent developments in the regulatory climate for biotechnology in the UK, centred mainly on a willingness to deregulate the industry and develop systems for self-regulation, are very welcome. There is no doubt that the perception of many multi-national pharmaceutical companies has been one of disinvestment in Europe when faced with what increasingly appears to be a dwindling science base and a reluctance of the regulatory authorities to accommodate new therapeutic approaches. A perceived unwillingness to lead the world in exploiting new genetic knowledge will have a major impact on Europe's future competitivity in the health-care market. This in turn will lead to increasing out-sourcing of biotech manufacturing and research capabilities, which in the long term will undoubtedly affect both the employment prospects and the quality of care available to our citizens.

5. *What is the involvement of your company in genetic research?*

Pfizer has made a major commitment to genetic research, investing worldwide, many hundreds of millions of pounds in developing its biotechnology base, primarily in support of its drug discovery operations. We have several products in development based on this research, representing approximately 10 per cent of our current portfolio. The prospects of future investment in this area are very favourable, and we would expect to reap an increasing reward from such investments over the next decade.

The development of such genetic therapies will largely be driven from in-house initiatives, although leverage will undoubtedly be required for these from judicious external investments. As mentioned above, a major factor in developing new products is the degree to which patent protection is available, and we would look to securing a strong IPR position, whether this is primarily through in-house research, association with academics, or through liaisons with other industrial companies.

Pfizer is a multi-national company which carries out its research and development using a number of criteria to determine where. Two of these criteria are where there is a strong scientific base, and a favourable regulatory regime.

6. *Is the UK a good place to carry out such research?*

The UK has the potential to be an excellent location for genetic research. The scientific infrastructure is one of the best in the world, and the quality of British science in the area of molecular biology is extremely high. Current investment in such infrastructure through the Wellcome Trust and, to a lesser extent, the MRC and

BBSRC must be encouraged, as should the continued investment in UK of multi-national pharmaceutical companies such as Pfizer.

Memorandum from Zeneca Pharmaceuticals (HGC42) (9 December 1994)

1. Knowledge of gene(s) fundamentally associated with a particular disease can provide substantial help both in drug design and therapy, e.g:

— The gene product (e.g., receptor or enzyme) can be used directly for in vitro screens to identify novel drugs.

— Gene products can be used for structural analysis and rational drug design.

— Knowledge of the gene will, in the longer term, enable novel approaches like antisense and gene therapy to be developed. In addition, knowledge of genes predisposing to disease will allow accurate diagnosis and identification of "at risk" populations.

2. There will be differences between conventional small molecule therapy and gene therapy, especially in the design of the research programme for drug discovery and drug formulation for delivery.

3. The issues surrounding development of gene therapy products will be similar to those already encountered by the pharmaceutical industry in the development of recombinant products (Biopharmaceuticals). It is likely that initial development costs of gene therapy will be high because of the multi component nature of the therapies which are being considered for major diseases. However, the semi-generic nature of gene delivery and regulation systems should reduce these costs in the medium to long term. This will obviously reflect on the cost of treatment.

4. Diagnostics is likely to play an ever increasing role in drug development as well as in defining the target population for treatment (see flowchart).

5. Due to the substantial costs and risk associated with the discovery and development of novel drugs, patent protection of key components having specific utility in drug discovery and development processes do play a significant part in influencing commercial exploitation. Efficient technology transfer can sometimes play an important role.

6. Genetic modification regulations in the UK are strict and compliance does impact on research costs. However, pharmaceutical manufacture and development is already performed at a level which meets internationals standards.

7. Zeneca Pharmaceuticals recently launched a Genome Initiative with the aim of gene discovery as well as gene based product development in the future. This work involves world-wide collaborations with academia and commercial alliances.

8. Zeneca's Cellmark Diagnostics business has recently completed development of its first genetic test to detect carriers of Cystic Fibrosis. It is already in use in some UK centres and a range of other tests for genetic disorders is in development. However, it is clear that much education needs to be carried out so that appropriate genetic counselling of patients and their families can take place.

9. Yes. However, the level of research funding needs to ensure a competitive scientific base within the UK. In addition a much greater level of interaction between academic research and industry should be encouraged to allow a clear appreciation of the needs and requirements of both parties. This will enable timely commercial exploitation of British inventions.

Memorandum from Dr R K Craig, Therexsys Ltd, University of Keele (HGC44) (9 December 1994)

Thank you for asking Therexsys Ltd to submit evidence on the Committee enquiry into Human Genetics. I would like to address your specific points as follows:

1. The identification of genes associated with particular diseases will provide new opportunities for the diagnosis of human diseases. Early diagnosis of inherited or acquired human diseases will lead to the increased likelihood of effective treatments using available drugs. This will be of particular importance in diseases such as cancer where early detection will lead to improved chances of effective treatment and prolonged disease free

interval, and in certain inherited diseases where improved management of lifestyle (e.g., diet), may lead to a better quality of life, and greater life expectancy.

Knowledge of the detailed structure of disease causing genes and the proteins they encode will allow scientists and clinicians to determine the molecular basis of disease processes, and so devise new medicines. Understanding of the structure, function or regulation of expression of the causative gene product (protein) provides numerous possible avenues to devise new therapeutic approaches. This can be via medicinal chemistry approaches or alternatively via recent advances in the development of gene based approaches, by which causative genes may either be corrected, or alternatively, their expression modified or eliminated.

2. The development of gene based medicines differs little in concept from conventional medicines. There remains the requirement that the gene must be delivered to the correct site of action in the body, and that expression of the gene must be regulated in response the specific physiological control mechanisms of the body, or by orally active medicines. The specificity of gene delivery in combination with controlled expression ensures that unwanted (toxic) side effects are minimised. It is likely that the first gene therapeutics will be used to treat cells removed from the patient, which after gene modification will be returned to the patient. Therexsys for example is focusing its attention on the treatment of cells present in blood. The removal and replacement of blood is well established technology used universally in hospitals throughout the country. Alternative routes of delivery under development include nasal sprays, direct injection and oral uptake by cells of the gut.

It is probable that the development time of the first gene therapeutics will be shorter than conventional medicines. This primarily reflects the choice of target, life threatening diseases, where no alternative treatments exist. In such circumstances promising drugs will move rapidly through the clinic to the marketplace. Once safety and efficacy of the early gene therapeutics has been established, applications for chronic disease (e.g., inflammation) will have longer development times since comparative trials will be needed to assess advantage over existing drugs already on the market. Overall one would expect shorter development times with associated savings in development costs. How this will be translated into treatment costs will depend on the disease in question, and the number of cycles of treatment required. Where gene therapy leads to cure (e.g., genetic diseases), or better disease management with reduced side effects (e.g., AIDS), then one would anticipate an overall reduction in health costs, and a marked increase in the quality of life.

3. Strong intellectual property is essential for competitive advantage. In the absence of strong Intellectual Property, it is virtually impossible to secure funding for new high risk ventures such as Therexsys. In general UK scientists working in academic centres of excellence remain blissfully ignorant of the commercial value of their work, and are often resistant to their own involvement in filing and protecting their own inventions. This is in contrast to the US where there is a much greater awareness of the potential commercial "value" of inventive research in the Biological Sciences. In the UK, technology transfer facilities are of mixed value. The best of them understand the value of strong intellectual property, and can realise true commercial value. The worst fail to provide adequate protection of Intellectual Property, and provide little assistance in commercial negotiations. The MRC and CRC technology transfer groups stand out, and have the advantage that they have sufficient funding available to pay the considerable costs necessary to file and maintain key intellectual property. There are some well funded University technology transfer groups (e.g., Imperial College) staffed by professionals, however this is the exception as opposed to the rule. Many smaller Universities lack the funding for staff to ensure adequate protection of Intellectual Property and consequently exploitation of their inventiveness.

4. The regulatory regime for genetic-based industry in the UK is at present evolving as in most European countries, and draws heavily on experience gained from earlier US studies. The approach is careful, considered, and responsive in its attitude to the application of gene based medicines. Greater attention is rightly placed on ethical and safety issues in the formative phase of the industry, but there is no reason to believe that the overall regulatory process will differ significantly from that of an orally active small molecule, the present gold standard for the industry.

The availability of Venture Capital funding is of greater concern. There are two significant issues—people and exit routes.

There is a critical shortage of suitable qualified professionals in the UK willing or able to manage high risk ventures. This may simply reflect a low entrepreneurial gene pool, or a view that the risk/rewards ratio remains unfavourable for taxation reasons. The professionals cross the Atlantic and rarely return.

Investors need exit routes to realise gains on long-term high risk investments. The recent revision of the Stock Exchange rules affecting the floatation of early stage Biotechnology companies has done little to encourage investment in the UK as opposed to the USA. The bulk of UK funds in the biotechnology sector continue to be invested outside the UK.

5. Therexsys is committed to the development of safe regulatable non-viral gene delivery systems for the treatment of life threatening and ultimately chronic diseases. The company was set up around Intellectual Property licensed in from the Medical Research Council in return for a equity in the company. Currently the company plans to initiate its first clinical trials in late 1995 or early 1996. This will allow the evaluation of the safety, efficacy and competitiveness of Therexsys core technology. The establishment of a core technology

platform we hope will lead to the development of new treatments for a wide range of life threatening and chronic diseases at present poorly treated by conventional therapies. Our competitiveness is entirely based on Intellectual Property licensed in from MRC supported laboratories, or developed in-house, combined with strong working relationships with academic centres of excellence in the UK and Europe. With success we will develop as a global business through alliances with established pharmaceutical companies. We would hope that the focus of our activities remains in the UK. This will depend on our ability to raise finance in the UK to support the rapid expansion of R&D and associated manufacturing plant, between now and 2001 the predicted launch of our first product(s).

6. The standard of research in the UK in the biological sciences and in particular human genetics remains of the highest quality. This should not be regulated or directed in any sense, though the provision of a gentle steer encouraging groups to address specific problems of human health is not a bad thing. The best laboratories remain well funded, though new money for the creation of new initiatives is in short supply, and but for the significant contributions of the Wellcome Trust would be grossly inadequate. From a company view point the UK remains a very cost effective place to conduct R&D.

I hope the views set out above prove of value to the Committee. My overriding vision of the human genetics revolution, is that managed in a flexible and sympathetic manner with due concern for public concern, that there can only be benefits, and that these will impact significantly on the management of human healthcare within the next 10–15 years. Ethically the most immediate concerns are probably related to the speed and sensitivity of gene based diagnostics, particularly where these lead to predictions of reduced life expectancy or poor quality of life. Once gene therapeutics provide a route to disease modification, social and ethical issues associated with adverse diagnosis of presently incurable or unmanageable diseases will recede.

Memorandum from the Clinical Molecular Genetics Society (HGC45) (7 December 1995)

Note: The CMGS is a professional organisation of scientists working mainly in hospital diagnostic laboratories, and hence represents the main group of people presently applying the new genetic techniques to individual patients.

1.1 Very little. Understanding that many, probably most, human attributes depend on an interplay of genetic and environmental factors, neither of which operates in isolation, is sufficient general principle. The important factors are social and political policies. Decisions about the use or regulation of specific genetic information may depend on the exact nature of the information.

1.2 Yes—although of course research funding bodies are not the only interested parties.

1.3 Yes, in principle a research topic might be properly banned. Generating human-animal hybrids (as whole organisms) might be an example. Human behavioural genetics is emphatically not. The "unacceptable moral consequences" here come from people at both political extremes naively or deliberately drawing false conclusions from the science. Geneticists need to think beyond their immediate goals, because they are the people best placed to understand and explain the wider consequences and also because they are the first people to suffer if stupid limitations are imposed on them (e.g., in Germany geneticists suffer badly from ill-informed political regulation of laboratory procedures). Regarding hidden agendas, we can confidently say there are no hidden agendas in public-sector science, because everybody's career depends on publication of their results. Pharmaceutical companies no doubt have their secret strategic plans in this as in other areas.

1.4 Research into human behaviour is potentially extremely important. Given that behaviour is a crucial key to biological success, it is obvious that natural selection has been centrally involved in shaping human behaviour, and therefore that genetic factors are very important in human behaviour. For some people this basic truth has replaced sex and death as the great social taboo. It is interesting to debate why this should be, but it would be very stupid to go along with that view. Society can only benefit by a clearer understand of what "psychopath" might mean and when that label should be applied—our present ignorance in this area is responsible for much injustice and suffering. A successful society is based on a realistic understanding of the factors which motivate good and bad behaviour. There is no reason at all to suppose that research into genetic factors would lead to a deterministic view of behaviour—we know perfectly well that most behaviour is modifiable.

It is clear that genetic intervention *could* substantially modify humans—one has only to look at the different breeds of dog (different in temperament as well as physique) to see what can be done with determined selective breeding. Such knowledge has been available throughout history and modern genetics does not significantly change this.

1.5 Any objections in principle to germ-line intervention are non-technical. The CMGS has not taken a position on this, and we would defer to society's decision.

1.6 The practical area would be commercial exploitation. Maybe this is not practical law, but we would like to see knowledge of the DNA sequence of the human genome (and all other natural genomes) declared a public asset. Companies could of course patent products based on that knowledge, but not the knowledge itself.

2.1–2.3 Improved education is essential. Otherwise decisions either get left to one or two professions, or are democratic but based on unrealistic hopes and fears (both of which are widespread). Since humdrum reality makes bad television, and since the number of well qualified science teachers in schools is small and falling, we see no easy solution. Maybe resourcing of teaching material for schools?

2.4 The tension between understanding and condemnation of unacceptable behaviour will no doubt always exist—though one can do both. Where genetics truly does explain some socially unacceptable behaviour, we should recognise it—but it is unlikely that much unacceptable behaviour has a purely genetic cause.

In far-right politics (especially in France and the USA) genetic arguments are already being used to justify reductions in social programmes. Most people understand that these arguments are wholly spurious, and are wheeled out only because they happen to fit the pre-existing views of political extremists.

2.5 See answers above.

3.1 This is an interesting area. Research groups identify a gene, and pilot application of their knowledge to diagnosis. But they do not have the funding, organisation or interest in continuing a diagnostic service once the research potential is exhausted. In the UK (but less so in some other places, e.g., the USA) molecular genetic diagnostic laboratories are usually closely associated with university departments, have a high ratio of scientists to technicians, and are well able to move tests from research to service. Funding is necessary to help the transition. In the past this has been done, for example through Special Medical Development funds from the DoH; it will be important to ensure that similar funding is available in the future, e.g., through Health Service Research funds.

Some genetic diseases are so rare or heterogeneous that each diagnosis is in effect a small research project, and there may be difficulty finding a lab to do the diagnosis. The CMGS operates a voluntary consortium scheme which helps ensure that services are established for the more obscure diseases. For some genetic changes, development of services may lag either because the counselling implications are not clear (FRAXE might be an example), or because it is debatable whether DNA techniques are the most relevant (hypercholesterolaemia might be an example).

3.2 No (except in the degree of potential public misapprehension).

3.3 We think genetic information should be confidential. The principle is the same as not allowing employers to refuse to take on young women, who might want maternity leave some time in the future. Decisions on employment should be based on present capacity to do the job. Both employers and insurers would naturally like to be able to take on only "good risks". This is a quite proper wish for them, but its application would be against the broader interests of the society. This requires legislation. Legislation would protect the interests of individuals, but also protect employers and insurers by creating a level playing field, on which their competitors could not gain an advantage by applying genetic testing remorselessly.

3.4 There is a large body of work and a general consensus on when population screening is appropriate. The key point is that it should lead to some useful action (not just denying somebody employment or insurance). The action must be socially, legally and ethically acceptable, and the screening programme must represent a good use of resources for which there are many competing claims. There are also technical requirements of sensitivity and positive predictive value.

3.5 See 3.3

3.6 For families with mendelian diseases segregating, e.g., Huntingdon disease, failure to disclose the history might be seen by the partner as showing a lack of frankness in the relationship. In general at present there is little value in checking the suitability of the partner as breeding stock, whether scientifically or otherwise, and for many people the idea would be repugnant. This is an individual decision, the proper concern of the couple but not of Society.

4.1 So far not much, but understanding the basic pathology must be the best hope of designing better treatments. Drug development has always been a long process, for good reasons. It is the contrast with the extremely rapid pace of genetic science that gives an incorrect impression of failure. Although treatment has not yet benefitted much, the range of options open to families is often substantially improved by knowledge of the gene. Prognosis may also be made more reliable by dissection of genetic heterogeneity.

4.2 We do not see somatic gene therapy as different in principle from other therapies.

4.3–4.4 Difficult for the CMGS to give informed comment.

4.5 One could imagine veterinary drugs, cosmetics (remedies for baldness etc). The technology would no doubt have other applications, and there is also a spin-off in informatics.

5.1 Scientific projects are potentially worthwhile if the information they provide is either fundamental or useful. Sequencing the human genome would be both. The nature and function of genomes, especially ours, is

by far the biggest unanswered but answerable question open to science at present. It can be answered for a modest price and the answers would provide the material for the next century of biological science and biotechnology. Although in funding terms sequencing (not just mapping) expressed genes is clearly the priority, it is simply unrealistic to imagine never finding out what is in the rest of the DNA. If there are surprises in the genome, that is where they will be; many evolutionary problems also require this sequence.

5.2 What makes us human is our whole genome. Knowledge of parts of it is partial knowledge—valuable but incomplete. Comparative genome studies require complete genomes. In the end it is not realistic to imagine the business will remain forever undone—the only question is what priority should be given to completing it as quickly as possible. In practice progress is likely to be exponential, as technologies mature. Stopping at the 50 per cent of the cost.

5.3 There is no general answer to this. Both genes and environment are important, and they interact in subtle ways. Phenylketonuria (PKU), a purely genetic condition for which newborns are screened, is an example. If a child ends up mentally retarded because of PKU, the explanation is the environmental (a mix-up in the screening, didn't stick to the diet etc). Popular comment usually overemphasises genetic determination ("the gene for homosexuality".) and fails to appreciate the interaction.

5.4 We think we understand, but extensive animal experiments are an absolute requirement. This is one area where popular suspicions may be quite helpful in restraining enthusiasts, because everybody understands that one disaster would unjustifiably set the field back for years.

5.5 The research councils and charities probably have a good appreciation of the importance of human genetics, but there is a limit to what they can do when general funding is such that alpha-rated proposals often have to be turned down.

6.1–6.7 Genetic research promises to tell us a great deal about how human evolution happened, but offers negligible scope for intervention, accidental or intended. Environmental change is vastly more important than genetic change over a timescale of decades or centuries. For genetic selections to have an effect over only a few centuries, each generation would have to be the offspring of only a small proportion of the preceding generation. The political and social regime required to enforce this would be a far greater cause for concern than any genetic consequences of such a programme.

Memorandum from The Royal College of Pathologists (HGC46) (8 December 1995)

The remit of the committee is very wide. This response is limited mainly to issues associated with the laboratory diagnosis of human genetic disorders.

1. GENERAL ETHICAL AND REGULATORY

The important issue of whether it is ethically acceptable and economically necessary to patent human genes which have been cloned by academic or commercial organisations is deserving of detailed consideration by the Committee. The question of patents is listed under "economic benefits" (section 4.3). This should also be considered by the Committee as a potential hazard to the provision of genetic services. The cloning of a gene associated with predisposition to a genetic disease is generally the culmination of an intensive international effort by many laboratories, funded from a wide variety of sources, including governments, private research charities, and commercial companies. The final step in the cloning process is the actual isolation of the gene from a narrowly defined region of the human genome. It does not seem ethically sound that the laboratory or company which is the first to achieve this final step should be entitled to *sole* commercial "ownership" of the gene. Furthermore, the patenting process relates to novelty and invention. Whether a laboratory can claim to have *invented* a gene which had been known to exist since the genetics of the particular disorder were first described seems highly debatable. An attempt is now even being made to extend this principle to the patenting of as yet undetected mutations in the breast cancer gene, BRCA1![1]

The consequence of continuing to allow the international scientific community to patent gene sequences could be a substantial escalation in the costs of providing tests for genetic disorders to the NHS. Some NHS laboratories have already received demands for royalties. There should at least be some provision for the exemption of non-profit making organisations from such royalty payments. There is no evidence that *not* patenting genes associated with genetic disorders has inhibited the genetics community from devising tests for patients or from exploring opportunities for gene therapy.

2. *Public awareness and education*

The explosion of genetic information that has occurred in the past five years has resulted in the availability of a wide range of new tests for genetic disorders, and created a new series of moral and ethical issues which a significant proportion of the general public will have to face at some time in their lives. These include questions as to the advisability and consequences of presymptomatic predictive tests for adult onset disorders such as Huntington's disease and breast cancer, and the question of how severe a genetic disorder needs to be to warrant prenatal diagnosis and possible termination of an affected pregnancy. Such issues will multiply as genetic information continues to expand, particularly in the area of predisposition to common disorders such as heart disease, diabetes and cancer.

The extent to which secondary schools provide education in the basic principles of genetics and in the impact which genetic disease and genetic information may have on members of the public should be assessed and very probably strengthened.

3. *Genetic disease*

3.1 The conversion of new genetic discoveries from a research activity to a routine medical service is often accomplished quite rapidly. However, two important questions need to be addressed in order to ensure the provision of a high quality, comprehensive, national diagnostic service. These are :

(1) the provision of adequate research and development funding which is needed to establish a new service, and

(2) rational organisation of the service at a national level.

In the aftermath of the discovery of a new disease gene, a substantial number of genetics laboratories may set up testing for the disorder, which can lead to the provision of services with a wide range of sophistication and expertise, and of sample load. Thus resources are used without regard to economies of scale, or to the benefits of provision of an expert service by a limited number of centres. This fragmentation of effort has been further encouraged by the purchaser/provider system in which laboratories seek to protect their viability and independence by offering as wide a range of services as possible. The funding for the initial setting up of these services has traditionally been provided by the research charities. However there is now an increasing reluctance on their part to fund what are perceived as legitimate NHS service developments. Some R&D funding is being made available through locally organised schemes, but there are many claims on these funds, and they are consequently inadequate to support much of the R&D requirements. In addition to the provision of new services, a continual process of evaluation and development of new cytogenetic and molecular genetic techniques is required to maintain a state-of-art laboratory service.

What is required from the purchasers is recognition that genetics is currently moving forward at a very rapid pace, and that there is thus *constant* need for the provision of funding for R&D within a service laboratory. Furthermore, it would be very helpful if the Department of Health were to consider the establishment of a standing advisory genetics committee to consider the implications of all new discoveries in the field, and to find ways of rationalising the provision of services such that a limited number of centres provide an expert service with a relatively high sample throughout.

3.4 Population screening for genetic disorders is widely regarded within the genetics profession as being appropriate if the disease is relatively common in the population, if it is severe and without effective treatment, if it is technically feasible to screen large numbers of samples with acceptable accuracy and sensitivity, if it is offered to the public in a non-directional way, and if adequate genetic counselling is available to explain the results of the test to families with a positive test. Successful models for such screening exist in the Jewish population (for Tay Sachs disease) and in the Greek population (for thalassaemia) which have had a significant impact on reproductive behaviour and consequently on the incidence of these disorders in these populations.

The majority of the population of the United Kingdom have a carrier risk for cystic fibrosis (CF) of 1 in 22, and approximately 300 children per year are born with this disease. Similarly, persons of Afro-Caribbean descent are at high risk of being carriers of sickle cell anaemia. Despite the fact that numerous pilot research studies were published during 1992–93 showing that carrier screening for CF can be effective and is well tolerated, and that cost/benefit studies have shown that screening would be beneficial even in financial terms, there is no evidence that a national screening program is likely to be introduced. This stems partly from a concern that both laboratory and clinical resources will be inadequate for the task, but also from the lack of a national organisation which could:

(a) Decide that such a program was necessary.

(b) Lobby for its introduction, and,

(c) Establish guidelines and regulate its conduct. The introduction of such screening programs could be included in the remit of the standing advisory committee proposed above. Indeed, the Nuffield Council on Bioethics has proposed such a committee in its report on ethical issues in genetic screening.[2]

5. *Research*

5.1 At least one powerful argument in support of mapping and sequencing all of the genes in the human genome (as opposed to sequencing the entire genome) is the speed with which it will be possible to isolate disease genes once they have been mapped to a particular chromosomal region by genetic linkage techniques. The temporal gap between the mapping of the gene and its cloning is often long (e.g., 10 years for Huntington's disease). Once all of the genes in a particular interval have been identified and sequenced, likely candidates for a disease gene which has been mapped to that interval can be selected and rapidly tested for mutations in affected individuals. This will be particularly important in the identification of genes which predispose to common disorders, since for technical reasons involving the complexity of the genetics of such disorders it is much more difficult to narrow the candidate region to a small interval.

REFERENCES
[1] Nature, 10 November 1994, p. 118.
[2] Genetic Screening, Ethical Issues. Nuffield Council on Bioethics. (London 1993).

Memorandum from The Nuffield Council on Bioethics (HGC49) (8 December 1994)

1. The work of the Nuffield Council on Bioethics, culminating in its report *Genetic Screening: Ethical Issues,* has covered much of the first three areas of the Committee's questions and has had a bearing on one of the questions on "economic benefits" (Area 4).

GENERAL ETHICAL AND REGULATORY

2. It seems appropriate to start with the Committee's first question about our knowledge of the way genes work and whether our knowledge is likely to be sufficient to make decisions on the use and/or regulation of genetic information. Research has so far built up considerable knowledge about single gene disorders. These are comparatively rare. The most common in north-west European populations is cystic fibrosis, with a birth incidence of 1 in roughly 2,000. Scientific research has made rapid advances recently in our understanding of the genetic component of diseases that are:

(1) Common: for example, some cancers, some heart disorders and diseases associated with old age such as Alzheimer's.

(2) Multi-factorial, that is the genetic component is but one factor that may influence onset, severity and ultimate prognosis: this appears to be the case with breast cancer.

(3) Late-onset: indeed, while the predisposition may be present, the disease may never manifest itself, or may do so only towards the end of a life that can reach normal expectation.

(4) Psychiatric: here the centrality of notions of human consciousness, personality and dignity will complicate the setting of guidelines to govern both research and its application.

3. These four aspects of recent scientific advance make it clear that what we need to know, when it comes to the use or regulation of genetic information, goes well beyond knowledge of the genetic mechanisms alone. For the human consequences of this scientific knowledge will require great care and much careful monitoring. Already we have built up experience of the handling of information in relation to single gene disorders such as beta thalassaemia, cystic fibrosis, Huntington's disease and sickle cell disease. All these four genetic disorders are comparatively simple, in that they are single-gene disorders that can be shown by genetic tests to be present or not. In all four cases we have needed to learn lessons from well-intentioned initial screening programmes. With beta thalassaemia the Cypriot government initially discussed, and then rejected, a compulsory programme. The issue was then taken up by the Orthodox church authorities. They instituted a requirement for screening that has drastically reduced the birth incidence, while maintaining the Church's opposition to abortion. UK pilot trials of population screening for cystic fibrosis have shown variations in the rate of acceptance of offers of testing: these variations need to be reviewed. After the cloning of the gene for Huntington's disease in early 1993, researchers were surprised by the relatively low take-up of tests among the families known to be at risk. The initial campaign in the 1970s in the USA to combat sickle cell anaemia has become notorious, possibly unfairly so.

4. Tests to reveal genetic predispositions that are common, multifactorial, late-onset and, in some cases, psychiatric are becoming available. It is for this reason that we consider that scientific advances in the year since the publication of the Council's report *Genetic Screening: Ethical Issues* reinforce *the recommendation that the Department of Health in consultation with the appropriate professional bodies formulate detailed criteria for*

introducing genetic screening programmes, and establish a central co-ordinating body to review genetic screening programmes and monitor their implementation and outcome.

5. As a contribution to the discussion of criteria for screening programmes, we suggested they should include the following:

(1) The aims and purposes of the entire programme.

(2) The predictive power and level of accuracy of the particular screening test.

(3) The value to those being screened of the knowledge gained. For each programme this should have been researched as an integral part of the follow-up to the pilot programme.

(4) The availability of therapy for the particular condition, accepting that lack of treatment does not necessarily mean that screening is not worthwhile.

(5) The potential social implications; and

(6) The resource costs.

6. This proposed coordinating body should undertake the following tasks:

(1) *Review of major pilot projects.* This would be an overview since we assume that research and pilot projects would continue to be referred automatically to Local Research Ethics Committees (LRECs).

(2) *Provision of guidelines*, if found necessary, to LRECs on criteria to be adopted in reviewing research and pilot proposals.

(3) *Monitoring*, on a continuing basis, major pilot programmes and the implementation of population genetic screening programmes. The aim would be to fund experience, and to review sensitive aspects of such programmes, such as:

(a) Good practice in giving information.

(b) Best practice in securing that consent is both real and voluntary.

(c) Maintenance of technical standards in quality control.

(d) Minimising undue anxiety among those being screened and among other members of their families.

(e) Best practice in the communication of test results; and, in particular,

(f) Reviewing the necessary practice of proper counselling and monitoring its results-covering, for example, how well the distinction is understood between carrying and actually being affected by a given genetic disorder.

(4) *Funding the experience* of the impact of genetic screening programmes as a guide to their future development as part of the health care services.

(5) *Review of the ethical, social and legal aspects* of the implementation of genetic screening programmes *insofar as such considerations affect the health of the nation*, for example:

(a) The implications for health of possible misinterpretation, or even abuse, of the results of genetic screening programmes.

(b) Reluctance to secure the health benefits of genetic screening because of implications either for employment or insurance.

Observations on the Committee's questions

7. The Council's observations on the other questions under this first heading can be stated more briefly. Prohibiting a research topic would seem at odds with the freedoms of a democratic society. Prohibiting certain *applications* of research might well be justifiable on moral grounds: a much discussed example might be human germline genetic engineering. It could well be that research in human genetics might lead some people to assert deterministic views of human behaviour. History suggests that such deterministic doctrines can flourish with or without evidence, based on a belief that the world might be improved through the abuse of genetic knowledge; hence the importance attached to the recommendations in paragraphs six and 10 of this Memorandum.

PUBLIC AWARENESS AND EDUCATION

8. We are in little doubt that public knowledge of genetics needs to be increased. In our report (paragraph 10.17) we stated:-

> "The threat of eugenic abuse of genetic screening requires safeguards. In a democracy, public understanding of human genetics should serve to create awareness of the dangers of eugenics, and of the possible stigmatisation of those carrying or suffering from genetic disorders. *We recommend that the*

need for improving public understanding of human genetics should be borne in mind in any review of the national curriculum and in the work of all public bodies concerned with the public understanding of science.'

9. Of equal importance is improving health professionals' knowledge of human genetics. Discussion of the Council's report at meetings held under the auspices of Regional Genetics Services has suggested that there is a major task in communicating appropriate genetic information to other medical specialists, to general practitioners, and to other professional health care staff. It is particularly important that the staff of antenatal clinics offering genetic screening should be adequately informed.

10. The Nuffield Council hopes that its recommendations on *adequately informed consent* (paragraph 10.4), on counselling (paragraph 10.5) and on the *confidential handling of genetic information* paragraphs 10.7–10.10) will be carried further in the elaboration of guidelines by the appropriate professional bodies, such as the medical Royal Colleges. The Department of Health will have an indispensable part in monitoring the adequacy of such guidelines. In our view this task should be undertaken by the body recommended in paragraph 4 of this Memorandum. In particular, the Department needs to take the lead in establishing guidelines on effective preservation of confidentiality, particularly in relation to genetic registers.

Observations on the Committee's questions

11. There is both general hope and general anxiety and suspicion about research in genetics. We see the task before the Committee not in terms of either justifying or allaying anxiety and suspicion. The Committee should rather see that the necessary framework is created for meeting reasonable anxiety and reasonable suspicion. Genetics has been abused in the past. We need to create institutions, procedures and, possibly, regulation to ensure that it cannot be abused in the future. The Council's report recognised (paragraph 10.18) that there were limits to the effects of educational work, however good. The Council, therefore, regarded as essential to the safeguards against eugenic abuse its recommendations on *adequately informed consent, confidentiality* and the *central coordination and monitoring* of genetic screening programmes. Guarding against eugenic abuse may be a long-term requirement, but these recommendations call for immediate action to enable people to respond to the impact and implications of genetic screening as presently organised.

12. There may be a danger that genetics will be seen as an excuse for socially unacceptable behaviour. But the limited research in this area, which has produced even more limited findings, cannot be sensibly interpreted as implying that genetics determines human behaviour.

13. Appropriate levels of spending on social programmes of health, education and welfare should be the stuff of politics in a democratic society. Research findings in genetics could be used by those seeking an increase in expenditure as easily as by those seeking reductions. In these matters, as more generally on the bearing of genetics on human behaviour, the Nuffield Council would advocate the careful assessment of research findings. Ethics and beliefs may have a bearing on the uses we make of research into human genetics. It is very difficult to see how human genetics could have a bearing on ethics and belief.

Genetic disease

14. The Committee's first two questions are not for the Council, although the Committee may find useful Chapter 3 of our report, which surveys genetic screening programmes in the UK as at September 1993. Gene therapy has not been reviewed in detail by the Council, which broadly accepted the conclusions of the Clothier report.

Information about an individual's genome

15. The questions posed about information on an individual's genome go to the heart of major issues that preoccupied the Council's Working Party. Employment is dealt with in Chapter 6 of the Council's report and insurance in Chapter 7. The report recognised that any recommendations over employment needed to balance employers' interest and employees' interests with the public interest. Similarly over insurance, a balance had to be kept between the viewpoints of proposers, of insurers and of health professionals. The latter feared undue pressure to be screened, inappropriate demands for disclosure of test results, the misinterpretation of results and the breaking of confidentiality. One question for the Committee must be whether these fears are substantial and, if so, where the public interest lies.

16. On *employment* the Council recommended *that genetic screening of employees for increased occupational risks ought only to be contemplated where:*

(1) *There is strong evidence of a clear connection between the working environment and the development of the condition for which genetic screening can be conducted.*

(2) *The condition in question is one which seriously endangers the health of the employee or is one in which an affected employee is likely to present a serious danger to third parties.*

(3) *The condition is one for which the dangers cannot be eliminated or significantly reduced by reasonable measures taken by the employer to modify or respond to the environmental risks.*

17. On *insurance* the Council recognised that the complexity of the issues required very careful discussion and exploration. The Council therefore recommended *that there should be early discussions between the government and the British insurance industry about the future use of genetic data, and that pending the outcome, the companies should accept a temporary moratorium on requiring the disclosure of genetic data.* Two exceptions were suggested to this moratorium to take into account the understandable interests of the insurance industry. These exceptions were:

(1) Where there was a known family history of genetic disease that could be established by conventional questions about proposers' families, then disclosure of the results of relevant genetic tests could be sought; and

(2) The moratorium should apply only to policies of moderate size. The exact limit would be a matter to be settled between the government and the industry in the context of arranging the moratorium.

In proposing a moratorium, the Council was following the example of the Netherlands where such a moratorium was established in 1990.

18. We share the Committee's worries about possible discrimination on the basis of genetic predispositions. The Council's proposals to guard against such discrimination are set out above at paragraphs 8–10. These proposals are designed to provide a sensible awareness and sensitive handling of the issues raised by the Committee.

Economic benefits

19. The Council has one major point only to make about the relationship of economic benefits and regulation. We do not see that they are necessarily opposed. The full and proper exploitation of the benefits of genetic screening depends on meeting the issues raised by anxiety and suspicion about research in genetics. The economic benefits will accrue not only in the commercial exploitation of research findings but also in the improvement of individuals' health. Preventive medicine should be able to make rapid strides if the benefits promised by genetic screening can be realised. The success of preventive medicine will create the commercial returns on the exploitation of the research. This will require a regulatory or quasi-regulatory framework that can be seen to operate in the general public interest.

20. There is concern that, in the absence of such a UK framework, "the UK may find itself responding to agendas or conclusions established elsewhere". These "may be influenced by viewpoints not widely held in the Uk, but which may nevertheless exert effects on the UK via EU legislation or other means". (Parliamentary Office of Science & Technology, *Human Genetics,* October 1994 p12)

Proposed UNESCO declaration

21. The Committee has asked what the proposed UN Declaration and Treaty on the protection of the human genome should say. The first draft of the Declaration was discussed at the second annual meeting of UNESCO's International Bioethics Committee (IBC) in Paris in September 1994. A copy of the draft is annexed.[1]

22. The Committee will observe that the present draft is in very general terms. In this respect it follows the Council of Europe's draft Bioethics Convention.

23. The Committee will be well aware that the UK is not presently a member of UNESCO. A UNESCO Declaration, and any subsequently proposed treaty or convention, would require the approval of the governments of the member states of UNESCO. This would be a matter for the biennial meeting of the UNESCO General Conference. Membership of UNESCO's IBC is on a personal basis, and two UK nationals are members: Professor Lachmann of Cambridge University, a past President of the Royal College of Pathologists and currently Biological Secretary of the Royal Society, and Mr Shapiro, Executive Secretary of the Nuffield Council on Bioethics.

[1] Not printed.

Memorandum from Professor Steve Humphries and others, Department of Medicine, The University College London Medical School (HGC51) (9 December 1994)

Screening for Cardiovascular Disease

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The memorandum has been drawn up with a focus on the work going on in our laboratory and elsewhere, to use the new genetic technology to identify individuals at risk of coronary artery disease (CAD) and to develop novel means of treatment. We describe the current state and direction of the science and the time scale of its application, and we discuss the financing of the work and its regulation.

Background

CAD is multifactorial with many genetic and environmental factors contributing and interacting. With the current state of knowledge, individuals can already be identified with a high CAD risk profile, such as those who smoke, who are obese, who have high blood pressure and diabetes, who have high LDL cholesterol and low HDL cholesterol, high Lp(a), or high fibrinogen. However, this information is not specific enough and within this group of high risk individuals only some will develop premature CAD, while others, for reasons currently unknown, are protected. Conversely, premature CAD also occurs in those with few classical risk factors and reasons for this are also unknown. The hypothesis on which genetic screening is based is that novel information about specific inherited factors will increase the specificity and sensitivity of current screening strategies and thus allows targeted early intervention of those identified individuals which will allow them to reduce their subsequent risk of developing CAD.

Genetic Information and Classical Risk Factors

There are many genes involved in determining the level of any single risk factor such as plasma cholesterol, and it is inherently unlikely that "measurement" of any single gene will have more predictive value of an individual's *current* cholesterol levels than a single (and at the moment certainly cheaper) measurement of plasma cholesterol. However, genetic information may be a better predictor of an individual's *future* cholesterol levels (i.e., the rate of increase with age) or the way levels respond to factors such as hormonal changes (i.e., after the menopause) or following the development of disease (e.g., microalbuminuria, hypertension or diabetes). This "variability" concept may be particularly relevant for levels of fibrinogen (a risk factor for thrombosis) which is an "acute phase reactor" which increases markedly after injury or infection. Individuals with an exaggerated post-trauma increase in fibrinogen may be at particular risk of thrombosis, and if the genetic factors responsible for this could be identified it would add information to that of a single measure of plasma fibrinogen. In addition, it may be impossible to measure some important proteins because they are expressed only in early developmental stages (i.e., pre-natally) or in tissues that are difficult to biopsy (e.g., within the plaque or heart tissue itself). It may be much easier to measure the genotype of the individual, since this can be done in a small sample of whole blood, or even in the DNA present in the white blood cells from a drop of blood obtained from a finger prick.

The hypothesis is thus that knowledge of genetic variation that is involved in "control" of levels of risk factors and in "response" of risk factors to environmental factors, will complement and enhance the predictability of classical risk factors for identifying those at risk of CAD. The challenge is to find such genetic markers and to identify the interacting factors and the mechanisms of this effect.

Current state of knowledge

The critical role of genes is in coding for structural proteins and enzymes which enable the cell, organ or organism to maintain homeostasis in the face of the environmental challenges experienced. Coronary artery disease (CAD) and risk of myocardial infarction (MI) can therefore be thought of as being caused by the failure of the individual to maintain homeostasis, and this is complicated by the fact that it is a multifactorial disorder, with both genetic and environmental factors being involved to a varying extent in causing the disease in different individuals in the general population.[1]

Rare mutations of large effect. In some individuals, who occur rarely in the population, a mutation in a single gene has a major impact in the determination of CAD and risk of MI. Any relatives of such patients who have also inherited the mutant gene, are also at a high risk, and molecular biology techniques can be used to identify such mutations. An example of this is the disorder Familial Defective apolipoprotein B-100 (FDB), which is caused by a G-A change in the apo B gene, resulting in the substitution of Arginine, at position 3500, for

Glutamine.[2] This substitution reduces the affinity of low density lipoprotein (LDL) for the normal LDL-receptor, and results in slow clearance of the LDL leading to hypercholesterolaemia. This mutation is found in roughly 3 per cent of patients with a clinical diagnosis of familial hypercholesterolaemia (FH), and the frequency of carriers of this mutation is roughly 1/700 members of the general population in many countries in Europe. By contrast, about one in 500 individuals in the general population are carriers for a defect in the LDL-receptor gene, but over 150 different mutations have now been described[3] with each being present in only a few patients. In the relatives of those with FH some but not all of these can be correctly identified by a cholesterol measurement, while unequivocal diagnosis can be achieved using a genetic test. With current technology such as Single Strand Conformational Polymorphism,[4] identification of the specific mutation in any patient with FH can be achieved within a few weeks, and we are developing new methods to speed this up and automate the process. Preliminary analysis suggests that different classes of mutations are associated both with differences in plasma lipid levels and with possible different prognosis of disease.[5] A similar strategy could be applied to identify mutations in other genes where defects are associated with risk for MI. An example of this are mutations in the gene for lipoprotein lipase, which may cause familial combined hyperlipidaemia in some cases,[6] and recently we have identified two mutations that alter Asp9Asn and Asn291Ser, each present at a frequency of 2-3 per cent in the general population, but which occur twice as frequently in patients.[7]

Common mutations of small effect. For most individuals, risk is not caused by a single mutation, but is the result of the combined effect of environment and polymorphisms at a number of different gene loci. Examples of such genes that control plasma lipid levels are those coding apo E,[8] the LDL-receptor, apo B,[9] the apo AI-CIII-AIV gene cluster and the gene for lipoprotein lipase. Common variants have also been identified in genes coding for proteins involved in thrombosis and fibrinolysis; namely the genes for fibrinogen, Factor VII and plasminogen activator inhibitor-1.[10] All three of these proteins are risk factors for IHD and it appears likely that variation at these loci also predispose an individual to disease. Two examples of the approach will be presented here.

Apo E has a key role in lipid metabolism,[8] and there are three common isoforms found in individuals in the general population called apoE3, apoE2 and apoE4, due to two single base changes in the apoE gene. Individuals who carry the apoE2 allele tend to have lowest lipid levels and those with the apoE4 the highest. In a recent study of postmortem specimens, apoE genotype was shown to be significantly associated with differences in the degree of atherosclerosis in the aorta.[11] Studies have also recently been published which demonstrate a strong relationship between the development of Alzheimer's Disease (AD) and the presence of apoE4.[12-15] This variant is caused by a single base change in the apoE gene which alters amino acid 112 from cysteine to arginine, which increases the overall charge of the protein by one unit, and has been shown *in vitro* to increase the propensity of apoE4 to aggregate with the beta amyloid protein.[15-16] Roughly 20 per cent of the general population are carriers of the apoE4 allele, and current data suggests these individuals might be at a two to three fold greater relative risk of developing AD. Individuals who are homozygous for the apoE4 allele represent roughly 2 per cent of the general population, and they have a relative risk of developing AD of 8-19 fold and develop features of dementia 5-10 years earlier than those with the common apoE genotype.[14] These findings have important implications with regard to the ethical and confidentiality issues of "opportunistic" screening, which are hard to predict with accuracy in the light of increasing knowledge, but also demonstrate how the new technology may impact on health care in the future.

Recently, extremely interesting results have been obtained with two novel candidate genes. The first of these is the gene coding for angiotensin converting enzyme (ACE), which functions to convert angiotensin I to the vaso-active angiotensin II, and to inactivate the vasodilator bradykinin. The enzyme is predominantly located on capillary endothelial cells, but ACE activity is also detectable in serum. Plasma ACE levels are very stable within the individual, but there are large inter-individual differences, and studies have shown that ACE levels are mainly determined by variation at the ACE gene locus.[17] A insertion/deletion polymorphism in intron 16 of the ACE gene has been identified, with individuals homozygous for the deletion allele (roughly 35 per cent of the population) having plasma ACE levels roughly 60 per cent higher than individuals homozygous for the insertion allele. In a recent large MI case control study from Europe the frequency of the deletion allele was found to be significantly higher in the MI cases when compared to controls (0.58 vs 0.54).[18] When the MI cases were further divided into those with or without conventional cardiovascular risk factors (such as raised apoB or obesity), the frequency of the deletion allele was significantly higher in those without conventional risk factors compared to the others (odds ratio of 3.2 vs 1.1). A synergistic effect of an angiotensin-II type 1 receptor gene (AGT_1R) polymorphism with ACE genotype has also been reported.[19] Individuals homozygous for the rare AGT_1R allele (9 per cent of the population) who are also ACE DD have a roughly four fold higher risk of MI, and the effect is greatest in those with low BMI and ApoB (RR 13.3). Thus the ACE and AGT_1R gene polymorphisms in combination appear to be a novel and powerful genetic risk factor for CAD, and may be having a large impact in patients considered to be at low risk according to conventional criteria.

In the future, use of these and other such common polymorphisms of similar impact would produce a battery of genetic tests which could be used as a basis for understanding or determining an individual's genotype-specific plasma lipid levels. To analyse such genotypes in a rapid, cheap and efficient manner we have devised a number of "high-throughput" methods. In one, we have described[20] a very simple device and method to prepare and manipulate horizontal polyacrylamide gels. The open faced horizontal arrangement enables loading of arrays of wells. We have also designed a device which preserves the exact configuration of the 8 x 12 array, and enables

electrophoresis along a 71.6 degree diagonal line-of-sight between wells (MADGE, microtitre array diagonal gel electrophoresis), using either acrylamide or agarose.[18] This eliminates almost all of the staff time taken in set up, loading and record keeping and offers high resolution for genotyping pattern recognition. The nature and size of the gels allows direct stacking of gels in one tank, so that a tank used typically to analyse 30-60 samples can readily be used to analyse 1,000-2,000 samples. We have recently completed development of the MADGE method for ACE genotyping, allowing genotype to be determined on 1,000 DNA samples within 24 hours. MADGE methods are also applicable to determining AGT,R genotype, for example by ASOs or by allele-specific amplification techniques. This system opens a wide variety of possibilities for diagnostic and research genotyping centred around existent microtitre plate technology, and is in essence an electrophoretic counterpart to the microtitre plate.

Areas of uncertainty

For all these genetic factors, as has been stressed previously, their effect on phenotype is modulated both by the co-inheritance of other genetic variations and particularly by the effect of environment. This "genotype-phenotype" relationship is of major importance in using genetic tests, but in principle is no different from the interpretation of for example, moderately raised levels of γGT in determining the extent of liver damage, or moderately elevated levels of creatine kinase in trying to assess the risk of carrier status in a woman who has a brother with Duschenne Muscular Dystrophy. We therefore do not see the uncertainty of the genotype-phenotype relationship to be a major detraction from using genotype information in the appropriate way to predict CAD risk, but clearly there are areas of research which need to be carried out to validate and justify such use and to establish suitable formats for their utilisation in counselling and patient management.

Summary

There is a need for primary research, firstly to establish the framework and feasibility for nationwide, family-based case finding for carriers of mutations which case familial hypercholesterolaemia (FH)—estimated 110,000 carriers in the UK. To carry out large scale case-control and prospective studies to determine the relative contribution of specific genetic markers to identify individuals at risk of developing coronary artery disease (CAD) *over and above* the measurement of classical risk factors.

At the present time there appear to be very few ongoing research projects of a large enough size to address the points of interest in a rigorous fashion. A community based project to identify the relatives of patients with FH is running in Southampton at present, with molecular biology being carried out by Dr Ian Day and Professor Steve Humphries at University College London. We are aware of other similar projects in Manchester, and that discussion is under way for similar work to be carried out in the London area. Although a number of case-control studies and prospective studies have collected whole blood samples for future DNA analysis, at present such research is not funded and is in the planning stage.

The likely benefits and savings of the application of genetic technology to CAD diagnosis and treatment are high. Coronary artery disease remains the major killer of men under the age of 65, and is a large burden to the National Health Service, as well as a loss to the Treasury of revenue from earned income. Since individuals with FH, and those with particular high risk genotype combinations are at greater risk of CAD, targeting lifestyle such as dietary habits and exercise, or even lipid lowering or other forms of therapeutic interventions are likely to have minimal side effects for maximum benefit.

The timing of the research need is immediate. There are a number of technological advances that have occurred in the last year which allow rapid screening of specific mutations and novel mutations (e.g., SSCP, DDGE, etc.) and this means that an unequivocal diagnosis gives a solid foundation for family-based case finding as a result of a detection of a specific mutation. For combinatorial multifactorial genetic factors, there are already enough genes known where mutations are having a small but significant effect on risk levels to make such research a sensible proposition at the present time, and as high throughput methods for genotyping become available, novel and so far untested candidate genes will be an economic proposition for research.

Ethical issues associated with mutation testing for FH

Because FH is a treatable disease, molecular testing does not raise the issues of untreatable diagnosis seen in Huntington's Chorea, not the problem of reproductive choice seen for example with CF. Carriers of a mutation in the LDL-receptor or apoB gene have a genetic *predisposition* to hypercholesterolaemia and CAD, but this can be successfully modified by dietary means and drug therapy. The availability of DNA tests will only confirm the clinical diagnosis for the patient, and will have a major impact on the willingness and ability of clinicians to carry out testing in relatives since unequivocal results can now be obtained. The major issues therefore appear to centre on the psychological impact of the diagnosis and the benefits of treatment in terms of mortality endpoint in FH. Although the overall benefit of lipid-lowering treatment (lowering of lipid levels, regression of coronary lesions) appears clear,[21, 22] further research is needed to assess the other issues. Epidemiological studies have

resulted in the identification of many CAD risk factors as well as hypercholesterolaemia, and this information can be used to identify (groups of) individuals who because of their personal and biochemical characteristics are at high-risk. However, such information is not "individual-specific" and many such individuals may survive, while "low-risk" individuals develop CAD. The same situation is known to occur with CAD risk for individuals with FH, though exacerbated by the high plasma cholesterol. Identifying the additional risk factors is a major focus of on-going research in the UK and elsewhere.

There is some evidence that different mutations causing FH are associated with different levels or plasma lipids,[5] and may thus be associated with different levels of plasma lipids, and with different CAD risk. This may explain part of the familial aggregation in age of onset of clinical symptoms. The apoB mutation appears to be relatively mild, in part because VLDL remnants are cleared normally by apoE interaction with the (normal) LDL-receptors in FDB patients, both triglyceride levels and HDL levels are usually within the normal range, which may not be in the case for patients with LDL-receptor defects. Further research will be required to address these questions and should lead to higher quality of information being available to a patient with a specific identified mutation.

Currently, little is known about the psychological impact of a diagnosis of FH, though one small study identified no major difficulties in behaviour of children,[23] and highlighted ways in which greater family support might improve dietary compliance. Concerns might also be raised about the carriers being disbarred from life assurance or health assurance, although individuals requesting such insurance are usually asked for information about their own health and that of their relatives, and a medical check-up might include a determination of plasma lipid levels. Guidelines for this situation have been proposed by the Dutch Agencies and discussed recently,[24] and it seems reasonable to propose similar guidelines for FH. However, these issues will need to be addressed, and GPs will have a role on research to assess their impact, and in giving information to individuals who may be eligible for testing. One final issue is about contacting members of the family who are at 50 per cent risk or less of being carriers of FH, but who live at a distance, may not be in a regular contact with the nuclear family, and do not live in the same health district. Contacting such individuals "out of the blue" may raise medical and ethical problems, particularly if such individuals decline testing, and organising such approaches will in any case be cumbersome under current regulations for Ethical Committee approval for research protocols.[25] This problem may be overcome when such testing is "service" directed and not research, but the interim period will demand careful development. It is, however, an extremely valuable way to identify further carriers of FH,[26] and should not be dismissed unless these practical concerns cannot be appropriately addressed.

Value for money of research

There is a pressing need at this current time for support for primary research into the application of the genetic technology to CAD. The first aim should be to extend and develop the basis for region-wide and nation-wide case finding of relatives of patients with FH. This will require coordination, for example, of ethical committee approval across regional boundaries as well as the problems of ECRs for obtaining samples and carrying out measurements of lipids and genotypes. Primary research requirements for the multifactorial combinatorial research is to fund both affected-pair studies and prospective studies as well as case-control studies to understand better the genetic and biochemical factors contributing to the most useful combination of genetic markers and classical risk factor markers for identification of those at risk of premature CAD. The cost of these two research proposals is relatively small against the value of knowing the results. For example, the project in Southampton, funded by BHF and other charities for one clinical scientist, one lab worker and one research nurse has enabled the definition of the (high) levels of under-recognition of FH in families of 80 probands and has yielded preliminary experience with approaches to family tracing. For the combinatorial research, genetic studies can be "grafted on" to ongoing prospective studies (such as the Whitehall 2 Study being conducted by Professor Michael Marmot in London) or to case-control studies (such as ISIS-III being conducted by Professor Peto and Dr Collins in Oxford) and an estimate of the cost for postdoctoral fellow and research assistant for genotyping samples, even as large as 10,000 cases and 10,000 controls with consumables and statistical analysis would be £180,000 and take roughly 2–3 years.

It is likely that the undertaking of these two aspects of the work in the immediate future will have a major impact on the technological development of genetic testing for other multifactorial disorders of late onset such as diabetes, or dementia, and the better identification of at risk individuals who would have great impact in reducing overall mortality within the next 10 years. For example, it should be achievable to identify the vast majority of patients who are carriers for mutation in the LDL receptor gene (say, 20,000 families within the UK) within the next five years.

Gene therapy for CAD

Because there are several well tolerated lipid-lowering drugs available to treat individuals identified as being at risk of CAD, we have argued[27] that "gene therapy" methods (which are better called molecular therapeutic

methods) are not appropriate, except for specific cases such as preventing restenosis after angioplasty. The one exception to this is the rare cases of patients homozygous for FH, who occur at a frequency of roughly 1 per million. A report of an attempt to use gene therapy to treat such a patient was published earlier this year,[28] but this was not highly successful and the attempt has been criticised as premature by leading scientists in the field. In our view, the major therapeutic benefit that will result from the new genetic technology will be a better understanding at the molecular levels of the control processes involved in human pathology, and that these advances will allow new therapeutic modalities to be developed that do not necessarily involve gene therapy methods specifically.

Regulation

How should the research into genetics of CAD and its application to population screening and family tracing be regulated? There are some ethical concerns about the application of genetic screening and testing for disorders of late onset with multifactorial aetiology and clear gene-environment interaction such as CAD. A number of these concerns are common to other similar disorders such as Alzheimer's Disease, Hypertension and NIDDM, although the major difference is that for CAD there are powerful and generally well tolerated drugs which reduce an individual's subsequent risk of CAD, while this is not the case, for example, for Alzheimer's Disease, or Breast Cancer. However, there are a number of issues which need to be addressed, including the issues of confidentiality, the issue of "labelling" currently healthy people as carriers and the possible adverse psychological impact of this, and who, when and how to test on screen.[29]

Although there may be small local differences in the specific way these problems are dealt with, we propose that a National Council or Regulatory Board would be most appropriate to oversee the application of genetic technology in this area of human disease. The guide-lines drawn up recently by the Nuffield Foundation are useful in this regard and could serve as a model for a Regulatory Board. The main remit of such a body would be to examine, refine and approve detained protocols for the application. One advantage of having such a body would be to streamline the current Ethical Committee approval for protocols for tracing relatives, for example, of probands with FH, where extended family tracing quickly results in crossing District Boundaries, requiring new ethical approval. Such a regulatory Board might have as its primary remit the protocols dealing with the application of the technology rather that the initial basic research, which might more easily be dealt with under the current local Institute-based the ethical committee system.

Reduction of coronary artery disease is clearly a major plank of the health of the nation approach and targeting individuals who are at greatest risk of CAD is currently believed to be the most efficient and ethically justifiable use of scarce existing resources. CAD is found in all social and ethnic backgrounds and focusing on individuals with clear evidence of premature CAD and offering appropriate treatment and support brings this within the legal ethical framework which is widely accepted for the development of screening approaches.

References

[1]Goldbourt U, Neufeld H N. (1986) Genetic aspects of Arteriosclerosis. Arteriosclerosis. 6:357–377

[2]Tybjaerg-Hansen, A and Humphries, S E. (1992) Familial defective apo B100: a single mutation that causes hyperlipidaemia and premature coronary artery disease. Atherosclerosis, 96, 91–107

[3]Hobbs, H H, Brown, M S and Goldstein J L. (1992) Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. Human Mutation, 11, 445–446

[4]Gudnasson, V, Mak, Y-T, Betteridge, J, McCarthy, S N and Humphries, S. (1993) Use of the single strand conformational; polymorphism method to detect recurrent and novel mutations in the low density lipoprotein receptor gene in patients with FH: detection of a novel mutation Asp200-Gly. Clin Invest, 71 , 331–337

[5]Gudnason V, Day I, Humphries S E. (1994) Effect on plasma lipid levels of mutations in exon 4 of the low-density lipoprotein receptor gene in patients with familial hypercholesterolaemia. Arterioscl and Thromb 14:1717–1722

[6]Babirak, S P, Brown, B G and Brunzell J D. (1992) Familial combined hyperlipidemia and abnormal lipoprotein lipase. Arterio and Thromb, 12, 1176–1183

[7]Mailly F, Olivecrona G, Tugrul Y, Reymer P W A, Bruin, Seed M, Groenemeyer B F, Lansberg P J, Asplund-Carlson, Vallance D, Winder A F, Miller G J, Kastelein J M, Hamsten A, Humphries S E, Talmud P J. (1995) A common variant in the gene for lipoprotein lipase (Asp9 $\longrightarrow$ Asn): Functional implications and prevelance in normal and hyperlipidemic subjects. Arteriosclerosis and Thrombosis—in press

[8]Davignon, J, Gregg, R E and Sing C F. (1988) Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis, 8, 1–2

[9]Humphries S E. (1993) Life style, genetic factors and the risk of heart attack: the apolipoprotein B gene as an example. Biochemical Society Transactions for the Wellcome Trust Award Lecture. 21:569–582

[10]Humphries S E. (1994) The genetic contribution to the risk of thrombosis and cardiovascular disease. *Trends in Cardiovascular Medicine* 4:8–17

[11]Hixson J E, and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group: 1991. Apolipoprotein E polymorphisms affect atherosclerosis in young males. Arteriosclerosis Thrombosis 11:1237–1244.

[12]Corder E H, Saunders A M, Strittmatter W J et al. (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's Disease in late onset families. *Science*. 261:921–923.

[13]Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. (1993) Apolipoprotein E polymorphism and Alzheimer's Disease. *The Lancet*. 342:697–699.

[14]Saunders A M, Schmader K, Breitner J C S, Benson M D, Brown W T, Goldfarb L, Goldgaber D, Manwaring M G, Szymanski M H, McCown N, Dole K C, Schechel D E, Strittmatter W J, Pericak-Vance M A, Roses A D. (1993) Apolipoprotein E ε 4 allele distributions in late-onset Alzheimer's Disease and in other amyloid-forming diseases. *Lancet*. 342:710–711

[15]Strittmatter W J, Saunders A M, Schechel D et al. (1993) Apolipoprotein E: high-activity binding to {Eszett}-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer Disease. *Proc Natl Acad Sci USA*. 90:1977–1981.

[16]Strittmatter W J, Weisgraber H, Huang D Y et al. (1993) Binding of human apolipoprotein E to synthetic amyloid {Eszett} peptide: isoform-specific effects and implications for late onset Alzheimer's Disease. *Proc Natl Acad Sci USA*. 88:7389–7393.

[17]Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Sourbrier F: 1990. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest 86:1343–1346.

[18]Cambien F, Poirer O, Lecerf L: et al. 1992. Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. Nature 359:641–644.

[19]Tiret et al 1994 Synergistic effects of ACE and angiotensin-II type 1 receptor gene polymorphisms on risk of myocardial infarction. *Lancet* 344:910–913

[20]Day I N M, Humphries S E. (1994) Electrophoresis for genotyping: microtitre array diagnol gel electrophoresis (MADGE) on horizontal polyacrylamide gels (H-PAGE), hydrolink or agarose. Analyt Biochem. 222:389–395.

[21]Smith G D, Song F and Sheldon T A 1993 Cholesterol lowering and mortality: the importance of considering initial levels of risk. Brit Med J. 306:

[22]Scandanavian Simvastatin Survival Study Group (1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study. *Lancet* 344:1383–1390.

[23]Rosenthal S L, Knauer-Black S, Stahl M P, Catalanotto T J, Sprecher D L. 1993 The psychological functioning of children with hypercholesterolemia and their families. Clinical Pediatrics 135–141.

[24]Harper P S. (1993) Insurance and Genetic Testing. *Lancet* 341:224–227.

[25]Fost N. (1992) Ethical implications of screening asympotmatic individuals. FASEB J 6 2813–2817.

[26]Williams RR et al (1993) Documented need for more effective diagnosis and treatment of Familial Hypercholesterolaemia according to data from 502 heterozygotes in Utah. Am J. Cardiol. 72:18D–24D.

[27]McEwan J, Henney A M, Humphries S E, (1994) Vascular disease: the next target for local molecular theraputics. Brit. Med. J. 308:995–996.

[28]Grossman M et al (1994) successful ex vivo gene therapy directed to liver in a patient with F H. Nature Genetics, 6:335–341.

[29]Harper P R. (1993) Research samples from families with genetic disease: a proposed code of conduct. BMJ 306:1391–1394.

Memorandum from The Biochemical Society (HGC52) (8 December 1994)

1. General ethical and regulatory

1.1 We know a great deal already, we need to know more, but, yes, we are likely to obtain the information.

1.2 Yes.

1.3 Prohibition is probably not the right answer but geneticists (scientists) should (and do) think more widely. Scientists have shown themselves to be very sensitive in this respect. When recombinant DNA work first became possible a moratorium was put in place until it could be shown to be safe. It is hard to say that no one is pursuing a hidden agenda.

1.4 Possibly. Yes, they will try to improve the world in respect of humans as they already have done for plants and animals. "Improve" here is taken to mean stamping out debilitating genetic diseases that affect at least 3 per cent of births. Plant and animal breeding have been done for a long time by selection: now they may be done by transferring genes. If it were possible to cure individuals with sickle cell disease, cystic fibrosis, Tay Sachs disease, by a method that we fully understood and were able to control (i.e., understand consequences, how it works and not side effects) then some people will want to do it.

1.5 As last sentence to 1.4: if it could be done successfully at the germ line level, it probably would be done eventually if we had the perfect technology for doing it and understood the effects. It is hard to think of something as "wrong" if it could stop future generations suffering the misery of a genetic disease. However, it is understood that some will feel that this is treading on sacred ground, and scientists are well aware of these fears and indeed share them.

1.6 No answer offered.

2. Public awareness and education

2.1 There is quite a lot of knowledge of traditional genetics, there is also confusion and lack of knowledge about genetic engineering and what it can and cannot achieve. Steps should be taken at all levels in education to improve the information and understanding, but it is not something that is amenable to a campaign.

2.2. Yes, but only partly justified; more information and education, and transparent ethical control will help to allay. There seems to be a quite widespread public acceptance of somatic gene therapy, although there will always be some who oppose on principle. Germ-line therapy is quite different.

2.3 Probably, but who is going to do the tempering?

2.4 We hope not.

2.5 Don't know, but the answer is probably not a short one.

3. Genetic disease

3.1 Don't know, and probably yes. Some diseases are not being diagnosed because screening a whole population has a high cost and may not be justified where, for example, the disease is rare and/or untreatable.

3.2 Probably not, assuming the technology works well.

3.3 Should be confidential in the same way that medical records are confidential, but the questions about insurers and employers are very difficult ones.

3.4 For common diseases and where early treatment may be beneficial. But because there are many thousands of genetic diseases it will be impossible to screen for all: factors such as cost and availability of counselling and treatment must be taken into account. Unable to answer about organisation and regulation of screening.

3.5 No answer offered.

3.6 Yes, yes, yes (more diseases will be diagnosable).

4. Economic benefits

4.1 A great deal. An example is the use of antisense oligo nucleotides as therapeutic agents.

4.2 Ultimately probably not, but the technology needs developing. This will be expensive and companies will be involved who will then try to recover their costs. This is what happens now with conventional drug development.

4.3 Probably not much different from what happens with conventional drugs.

4.4 Unable to answer, but it is probable that investment may be lost to other countries.

4.5 Unable to predict products, but a great deal of information will be produced.

5. Research

5.1 Because it is there. The information will be valuable scientifically and commercially, including in treatment, and probably in ways that we cannot foresee. Both have potential advantages, but the sequence of the whole genome provides information on control and may reveal many new things.

5.2 Don't know, but you can only find out by doing it.

5.3 Unknown.

5.4 A great deal, but still a lot to discover. Yes, it is conceivable.

5.5 Difficult to say, but probably no.

6. Evolution

No answers offered.

Letter from Professor Timothy M Cox, Department of Medicine, The University of Cambridge School of Clinical Medicine (HGC53) (7 December 1994)

It was very kind of you to write on 1 December following a visit of Members of your Committee to the University of Cambridge Department of Pathology.

In your letter you raise the points about interactions between clinical scientists such as myself who are primarily concerned with understanding the pathological and molecular basis of particular human disorders and using this as a means to improve diagnosis and treatment and those involved, as at Kingston Hall, with large-scale sequencing and mapping. You also raised a particular question—perhaps rather a delicate one—about the possible exploitation of research which I have initiated using human tissue that was removed as part of a routine therapeutic procedure of a patient under my care in 1985. If I may I will elaborate on the details since it perhaps would put for you a rather different perspective on the celebrated Moore case?

To summarise, the patient's spleen was removed with his medical consent under conditions that were urgent and he has made a good recovery since the operation and is now receiving further treatment for his Gaucher's disease. After the operation, small amounts of the spleen were stored in liquid nitrogen and studied from time to time experimentally. The patient was aware of this and was pleased that his tissue was used for any further research on his condition. In 1988, it seemed to me that the spleen might act as a very good source for cloning a gene of scientific interest and so it was that my group managed to clone the particular gene. The results of this cloning and the characterisation and sequence of the gene as well as its mapping position were published in the European Journal of Biochemistry and hence no patent is possible for the sequence. Latterly, in 1990, as a result of the further experiments using the human gene, it occurred to me that the product of the gene, whose function, was hitherto unknown, might be involved in bone disease. As a result and with support through a scientific collaborative agreement modest salary support for a Postdoctoral worker to express the gene so that recombinant protein could be studied in abundance *in vitro* was secured. The object of this was to understand more about the structure and function of the protein which was of scientific interest to me and had the advantage that it would identify a new target possibly for the ultimate treatment of bone disease. Subsequently, the pharmaceutical company in no way prevented us from publishing a second substantial paper on the functional structural properties of the human gene product which appeared in a high quality American Journal this year. The company allowed publication freely and this, of course, prevents there being any successful patenting.

Because I have managed to interest the company in this protein they have undertaken to characterise it fully "in-house" using the most sophisticated techniques in molecular biology to determine its three dimensional protein structure. In our work we have phosphylated a mechanism for its mode of action and clearly the production of large quantities of protein will enable the company to begin the process of developing specific inhibitors for it, once with confidence it has been identified as a therapeutic target in man. We ourselves are continuing work on the function of this protein using transgenic studies in mice that have been supported in part

under the collaborative agreement with the company and our department and, although it would be my intention to inform the company of the results of these experiments, I would not anticipate any hindrance to our proposed publication of the findings.

While it is true that the partial sequence information gained from the clone that we had isolated using splenic tissue obtained from the patient has been of use in obtaining a full-length copy of the gene (on this occasion cloned from a commercial and anonymous human placental library) I do not think there is any chance that I will benefit personally from patent rights since the development of a useful therapeutic drug will be very much dependent on further research and development. In exchange for freedom to publish there can be no patenting and my academic endeavours only have profited. I think it would be difficult for the patient in this instance, even if he wanted to, to sue as successfully as Mr Moore had sued Dr David Gold. I would rather hold up the example to you as an example of true academic and scientific collaboration with industry which has the potential to develop a useful therapeutic drug and enhance scientific enquiry within the university hospital setting. I had occasion last year briefly with Mr William Waldegrave about this very piece of work and he was most intrigued by it and, when I next see the patient on his visit from Spain, I look forward to bringing him up to date as far as possible.

Memorandum from The Royal College of Surgeons (HGC54) (8 December 1994)

Thank you for your letter of 7 November, addressed to Professor Boulter who has now demitted office. On taking up the Presidency, I wrote to one of our senior Fellows in Edinburgh, Dr Malcolm G Dunlop FRCS, Senior Lecturer in Surgery at the Human Genetics Unit, Western General Hospital and asked for his views. I am now pleased to give our College response, based on these views, below:

1.1 Due to the method of identification of genes by positional cloning, many genes will be discovered without any understanding of the way the relevant gene works. There are already well established cases of genetics analysis being carried out without any need or regard to gene function. Examples include the genes for polyposis coli and colorectal cancer. Eventually the focus will move away from simply identifying genes and mutations within them to understanding their function and it is likely that the information will eventually become available for all genes.

1.2 The policies are by and large satisfactory with regard to ethical and social consequences. It seems likely that there will come a point when the enormity of the task of understanding what any particular mutation within any particular gene might mean in terms of future health and disease risk may overwhelm the ability to cover each aspect with an appropriate policy.

1.3 I personally do not believe that society has the right to prohibit research in certain areas simply because of perceived moral problems. Some individuals' moral stand point may be diametrically opposed to others. It should simply be the decision of the individual whether they agree to undergo tests or treatment involving genetics rather than being denied the offer of the tests in the first place. In practical terms it is impossible for geneticists and others in the field to think more widely than their immediate research goals due to the way research is funded and executed. I have no reason to believe there are any hidden agendas.

1.4 Research into human genetics itself does not lead to a deterministic view of human behaviour. I have no doubt that the aim is to improve the world through genetic intervention and I would applaud efforts to do so. Genetic interventions in this context could mean simply to identify those that are at risk of a disease which is eminently preventable by early diagnosis and/or treatment. I would however strongly argue against any move in the future to test for or interfere with any genetic conditions which could *not* result in a net benefit to the individual's health.

1.5 I personally have no fundamental objections to germ line intervention by terminating pregnancies in which it can be shown that the foetus has a serious genetic disorder, or indeed to selecting embryos on the basis of carrying a normal genotype. There are relatively few conditions in which this would actually apply. The principle of interfering with the germ line in a more positive way would not be acceptable in my own view or in the view of most of my colleagues. I think the term "playing God" is obviously an emotive one but it must be considered as a factor given that many of the public would consider this to describe any intervention with the genetic code. My own concerns are for the possibilities that any germ line interventions may result in integration of genetic material into inappropriate sites and result in effects which may not be manifest for generations.

1.6 The proposed UN declaration and treaty on the protection of human genome should amongst other things indicate that the genes or sequences, no matter how they are discovered, should not be patentable. There is an analogy with landing on the moon; we all know it's there; we can all see it but relatively few can land on it. This is already taking place and since we cannot patent the moon it seems highly inappropriate that any

particular gene should be patented by a research group who have been lucky enough to find it. An important second point that I would include in any declaration is that there should be a moratorium on active interference in the human germ line.

2.1 My impression is that the extent of knowledge and indeed the interest in genetics amongst most sectors of the public is minimal. In general the public understand little about most diseases and it seems to me that genetics should not be singled out for particular attention.

2.2 I think there is general suspicion about research in genetics mainly generated by the media. My own experience is that this is totally unjustified. Such suspicions should be allayed whenever possible and once again it would be wisest to do this through the media by a gentle education at an appropriate level.

2.3 I have no doubt that there are unreasonable expectations about the benefits that would come from genetic research. It is unlikely that it will result directly in dramatic changes in disease patterns since most diseases are related to degenerative conditions. Although gene therapy for conditions such as ischaemic heart disease and hyperlipidaemia may well be possible, it is unlikely that it would do more than delay the time of death, rather than completely cure the patient. Once again the expectations could be tempered through the media.

2.4 I see no danger that genetics could be used as an excuse for socially unacceptable behaviour except in a very few isolated cases. I would think that it may be possible that genetics could result in a shift of resources away from first aid type specialities such as surgery and hospital medicine to health education and social manipulation such as dietary changes. It is likely that this would result in an overall increase in health spending in the short to medium term.

2.5 I do not understand this question.

3.1 Genetic diagnosis is probably equally distributed between medical service and research programmes. The problem is that the continuity is not clear and that in certain cases mutation detection is between the two camps. It is neither research nor is it service commitment. This must be considered one of the major areas for attention in the introduction of genetic diagnosis into routine medical practice. There is no doubt that much progress could be made in certain diseases by taking away the notion that is a research programme, and develop a whole new area of funding which would be better termed "Development of genetic services". There are undoubtedly diseases with known genetic cause in which it is impossible to offer testing and diagnosis simply because of the enormity of the problem. One example of this is colorectal cancer. Current estimates suggest that about 3,000 cases arise each year in the UK as a result of mutations in certain genes. It would be possible to avoid the vast majority of deaths due to hereditary colon cancer simply by applying current knowledge to the entire population on a strategic basis.

3.2 I do not see any particular ethical questions about somatic cell gene therapy which are different from any other current medical intervention. The introduction of a therapeutic agent into a cell which is a chemical similar to, for instance, a neurotransmitter, is completely comparable with introduction of a sequence of DNA which happens to induce the cell to produce the same compound.

3.3 This is a very difficult question surrounding the confidentiality of information on a patient's genome. In most cases employers would not be concerned about the vast majority of information which may or may not be available. It is difficult to see any situation in which it would be possible to identify those individuals who are likely to be off work because of a specified disease within a specific time frame. However, I do not see employers as being a major problem. The insurance companies are already entering into this arena. The whole question of exactly what insurance should mean must be addressed to answer this question. Ideally, a modest insurance premium paid by a large number of people should be able to fund the health problems arising in a relatively small number. If certain individuals at very high risk pay an extremely high premium while others at a very low risk pay a very low premium, each of these population would eventually consider it inappropriate to carry on paying the premiums, for obvious reasons. This would result in the end of insurance as we currently know it. It does seem conceivable that the risks for a variety of diseases could actually be calculated at some time in the future and that this question could become reality. It seems to me that the government and the insurance industry as a whole should come to an agreement that insurance should, as I previously stated, consist of a modest premium for the whole population to fund the ill health of a relative few. The main concern would be to avoid those who were at high risk over-insuring themselves on the basis of knowing their own genetic risk of disease, as can already happen with disease such as diabetes and heart disease. The question of genetic testing is no different from current medical testing; it is only the potential breadth and accuracy of the analysis of future risk of various diseases that gives cause for concern.

3.4 Population screening for a genetic disease could only be considered appropriate when there can be net benefit to the entire population. It should be possible to intervene to avoid the potentially crippling diseases and the cost of the screening should be measured both in terms of finance and the morbidity associated with any such test. It is vital that easy and rapid access to counselling is available. The screening would best be organised on a regional basis and preferably be orchestrated by the genetics department identified as co-ordinating the effort in that area.

3.5 If screening were to become available for a range of genetic conditions, the current arrangements by which medical confidentiality is maintained should simply be extended to include information on genotypes. Individuals should be protected from discrimination because it seems likely that for most of the common conditions, genetics will only be able to indicate an increased risk of developing a particular condition rather than an absolute diagnosis. Thus an individual who, before testing, is perhaps at a population risk of 1 in 200, and whose test shows an increase in risk of 400 per cent would only have a 1 in 50 chance of developing the disease. The public might however, consider a 400 per cent increase a dramatic effect which should be discriminated against, when in actual fact the absolute risk is still very much in the individual's favour.

3.6 People would not be well advised to seek any genetic information from sexual partners on a routine basis, before conception of children. If there are specific conditions which are relatively common within the family, this is clearly a different situation. An example of this would be: the brother of a case of cystic fibrosis over whom there has been a great deal of heartache in the family, may be strongly against having any children which have a risk of developing cystic fibrosis themselves. It is perfectly acceptable that he may wish to test himself and if he carries the cystic fibrosis gene may wish to test his partner prior to conceiving children. It is possible that such testing may become prevalent as a result of future research but it is difficult to predict whether this will be the case.

Memorandum from The United Free Church of Scotland (HGC56) (8 December 1994)

The United Free Church of Scotland is grateful for the opportunity to contribute to the deliberations of the Science and Technology Committee.

We are conscious of the very wide remit of the committee and the range of questions which it hopes to address. We are also conscious of our lack of competence to comment on many of the issues under consideration. Having said that the Ethics and Current Affairs Committee of the United Free Church of Scotland (a standing Committee) takes a keen interest in the field of medical ethics[1] and has a developed overview on issues relating to the beginning and the end of life. Fundamental to our thinking is the uniqueness of the human person and our conviction that life begins at conception. In commenting on the vast field of inquiry of your committee we have therefore decided to be extremely selective and limit our input to a general consideration of your key question 4; "what are some of the social, ethical, and medical implications of this research?"

Firstly let it be said that we are not per se opposed to genetic research or the practice of genetic engineering. We believe that science is a tool created for the good of man and it can be put to benign or malevolent uses. Benign use includes the ability to prevent hereditary diseases and disabilities. We are aware that cystic fibrosis, Huntington's chorea, diabetes, Alzheimer's disease, and Down's syndrome, among others, may be traced genetically. If the initiative known as the Human Genome Project results in the successful treatment of some or all of these diseases we would regard that as a significant contribution to the human condition.

What are some of the ethical implications of research in the area of genetics? We believe this question can best be approached from the perspective of "personhood." One of the questions you are looking into is human evolution. This implies that humanity can be looked at as a species. In some respects this is true. However, our contention, having considered the options, is that each person is unique, and that the only reasonable point to regard that person being created is conception. We regard the fourteen day cut-off point for research on the embryo used by the Human Fertilisation and Embryology Authority as having no scientific, moral, or practical basis. We would agree with Tereasa Iglesias (Embryos and Ethics, Rutherford House Books, 1989) that "genetically speaking, conception is the formation of a new, unique, and completed genetic entity to which nothing is to be added for the next 70 years."

Furthermore the "person" is fundamental unity and totality which cannot be divided into independent parts. Theologically as well as biologically we can find no evidence that the "soul" or "spirit" of the person is added on at some particular moment in time. Conversely perfect knowledge of the genome or sum of all the DNA would still leave us ignorant of the aspect of personhood that makes us all unique. For example, would two cloned embryos produce two identical human persons? Theologically we would affirm the contention of the Old Testament psalmist: "We are fearfully and wonderfully made." (Psalm 139, v 14). A certain amount of godly fear is no bad thing in our view.

We suggest that the right questions to ask about genetic engineering and research relate to the end product. Is it being pursued to help eliminate identifiable genetic disorders? If that is the motive we believe the research could be beneficial. However if it is being pursued as genetic engineering in animals and crops is pursued, viz to produce a stronger or more vigorous strain, we believe it will prove counter-productive. Human nature will not be changed by genetic engineering if our hypothesis about the person is correct.

We would mention two consequences of the gathering of detailed information and of the capacity of science to obtain detailed information about the genetic make-up of individuals. Increased knowledge brings increased responsibility and we wonder about Society's ability to handle this knowledge. Firstly genetic screening in the prenatal area results in parents having knowledge about the unborn child's condition without having the ability to correct the genetic disorder identified. The resultant pressure to terminate the life of what we have argued is a human person is obvious. Secondly there is the area of confidentiality. Information about our DNA make-up is clearly very "personal" information. To whom should it be revealed? Should insurance companies have a right to know? Some of the principles of the Data Protection Act are relevant in this regard.

In conclusion we believe it is right to be cautious about the benefits that may accrue from research in the field of genetics and the benefits of the Human Genome Project. Given a world population of 5 billion or thereby we wonder how many will benefit from this research. However if the end view can be focused on the elimination of distressing genetically linked diseases such as those mentioned earlier, we believe the implications of research could be benign. We remain deeply concerned that continuing research will result in the continuing destruction of embryos (which we all were once) and that this fact alone casts a deep shadow over the potential benefits that research may facilitate.

We suspect we may have added nothing new to the large body of material at your disposal. However if you require further comment or if you wish amplification of any of the points we have made we would be most willing to co-operate in this most complex of fields.

REFERENCE

'The Ethics and Current Affairs Committee informs itself about developments in these areas primarily through subscription to the Journal of the Centre for Bioethics and Public Policy, 58 Hanover Gardens, London, SE11 5TN

Memorandum from Alzheimer's Disease Society (HGC58) (December 1994)

INTRODUCTION

The Alzheimer's Disease Society welcomes the Science and Technology Committee's inquiry into "Human Genetics". The Committee's investigation is timely in view of the recent scientific discoveries which have identified a genetic risk factor for Alzheimer's disease in older people. The increasing likelihood of a genetic test for Alzheimer's raises fundamental ethical, social and health issues.

Over the next 30 years Alzheimer's disease and other forms of dementia will be the major health and social care challenge in the developed world and its cost, both human and financial, will be vast. It is estimated that there are currently about 634,000 people with dementia in the UK. Approximately 70 per cent have Alzheimer's disease. As research progresses possible differential diagnoses are being made within Alzheimer's disease. Genetic research will contribute to this growth in understanding.

The majority of people with Alzheimer's disease are elderly. Age is certainly the dominant risk factor but it is estimated that there are some 17,000 people with dementia under the age of 65. Current research suggests that in younger people Alzheimer's disease has a predominantly genetic cause. Demographic changes mean that by the year 2021 almost 900,000 people will have dementia, of these, approximately 630,000 will have Alzheimer's disease.

EVIDENCE OF A GENETIC RISK FACTOR IN ALZHEIMER'S DISEASE

It has been known for some years that Alzheimer's disease in younger people has a genetic basis. Familial Alzheimer's disease is rare but the families who are at risk have been a major source of research data and their co-operation has been essential. Such families have experienced the human, clinical and ethical problems associated with other genetic disorders. However those which will arise should a predictive genetic test for late onset Alzheimer's be developed are of an entirely different order and have not been addressed on any other disease.

Until recently it was thought that Alzheimer's disease in older people was sporadic and not familial. Since 1993 research, originally published by Dr Alan Roses of Duke University and subsequently confirmed by others, has demonstrated a link between the E4 allele of apolipoprotein E and late onset Alzheimer's disease. Apolipoprotein occurs in blood. There are three main forms of apolipoprotein E. An individual may have any

combination of two of these forms inheriting one from each parent. Studies have shown that if two copies of ApoE4 are present there is a substantially increased risk of developing Alzheimer's disease in later life. It is possible that the ApoE2 allele is protective against Alzheimer's disease. A blood test can allow easy identification of which type of the apolipoprotein E is carried therefore opening up the theoretical possibility of a test to aid diagnosis or prediction of the risk of Alzheimer's disease in an individual.

Further scientific discovery is necessary to establish, for instance, those environmental factors which interact with this genetic information in such a way as to increase the chances of someone developing Alzheimer's disease. Despite this need, and the fact that Alzheimer's disease is probably the fourth largest killer after cancer, heart disease and stroke, Government funded research into Alzheimer's disease is now less than it was five years ago. In view of the possible benefits of genetic testing into Alzheimer's disease, the Society would urge the Government to increase research funding in the area.

Possible benefits of genetic testing

The significance of the ApoE4 research is that it places Alzheimer's disease within the growing number of genetically linked diseases and brings it within the frame of thinking about genetic screening, ethics and social policy.

There are important benefits to the individual of a predictive test for Alzheimer's disease—not least the ability to plan for the future. Individuals would be able to express choices about their financial affairs or medical treatment in the event of developing Alzheimer's. As our knowledge of the disease improves people may at some time also be able to benefit from prevention or delay, treatment, and in the long-term the possibility of a cure. Progress in research also depends on the co-operation of willing individuals who need to be confident that their participation in genetic research will be for their benefit or for the health gain of others.

These benefits may be put at risk by the commercial and political interests of purchasers and providers of health care, pharmaceutical companies and the insurance industry all of which would value access to genetic information on populations and individuals to enable more accurate long-term planning.

Consent and confidentiality

Whilst accepting the beneficial consequences of a genetic test for Alzheimer's, the Society recognises that there are a number of ethical dilemmas on which a more open public debate is necessary. These were recently examined by the Nuffield Council on Bioethics. One of the most important issues is consent included in the giving of consent. Consent should be fully informed and that assumes the ability to give consent.

In general terms, efforts to raise public awareness and understanding of Alzheimer's disease and of genetic testing, would play an important part in ensuring consent was informed. But proper genetic counselling should also be available at all stages.

Investigations by the Society have already revealed the extent to which younger people with dementia and their families and relatives, are denied access to such counselling. It has been known for some time that in a small proportion of those people who develop dementia in their 40s and 50s, Alzheimer's disease is caused by genetic defects. Yet 22 per cent of our branches report that they are unaware of, or have never had the opportunity to use the genetic counselling facilities provided by health authorities in their area.

The most important ethical consideration arising from genetic testing is who has access to and use of that information. Confidentiality is essential if the autonomy of the individual being tested is to be maintained. But this confidentiality will present dilemmas for medical staff when for instance genetic information is relevant to the lives of other members of a family, when an individual's control of the information may need to be over-ridden in the interests of another person. In the Society's view Guidelines in this area are essential to help clinicians and researchers in the field.

Discriminatory use of genetic information

Of increasing concern to the Society is the possibility that information gathered from genetic testing may be used to restrict an individual's access to life opportunities on the grounds of a perceived risk of illness and/or disability.

Confidentiality and access to information will also, for instance, be of interest to employers. Though in the case of late onset Alzheimer's disease this may not be of great significance, as we know more about the environmental factors which, interacting with a genetic susceptibility give rise to Alzheimer's in an individual, it may be that the work environment will become more important. Predictive tests might therefore become part of the standard health check for prospective employees.

The most contentious area, however, will be insurance—both life and health insurance and long-term loans such as mortgages. Whilst at present British insurance companies do not require genetic tests as a prerequisite for insurance, the Society's concern is that its use might become commonplace if it were possible to test for a high risk of more common chronic illnesses such as dementia. It is well established that insurance companies have discriminated against people assumed by them to be at risk of HIV infection. In view of the larger numbers of people affected by Alzheimer's disease, the commercial interest of insurers in avoiding such a high risk sector will be greater.

Equally, increasing overtures are made by policy-makers at both ends of the political spectrum about the likely value of reducing the public expenditure costs of long-term care by replacing it with a system of long-term care insurance or social insurance. Once again the Society would be concerned that genetic information might be used to discriminate against the very people who need such insurance cover.

Regulatory mechanisms

Genetic testing raises complex ethical dilemmas and has far-reaching health and social implications. Tests and the information revealed by them need careful management and control to ensure true benefit for the individual and Society.

A number of groups exist, bringing together clinicians, researchers and family members concerned with particular genetic disorders. An example is the Alzheimer's Diseases Genetics Consortuim established by the Institute of Psychiatry and the Alzheimer's Disease Society. It would be of great benefit if these were formally recognised by the Department of Health and a dialogue opened.

The Committee makes reference to the proposed United Nations Declaration as a possible regulatory device. The Society would recommend that particular attention is paid to the Bioethics Convention recently published for consultation by the Council of Europe.[1] The Convention clearly states the primacy of the interests and welfare of the human being over the sole interest of society and science. It asserts the importance of consent and confidentiality, and Article 17 reads "Tests which are predictive of genetic diseases or that may identify a genetic predisposition to a disease may only be performed for health purposes or for scientific research linked to health purposes".

The Society believes that if such ethical safeguards were approved and observed by governments they would go a long way to establishing a framework in which the benefits of genetic testing outweigh the problems.

Letter from Professor George Butterworth, The British Psychological Society (HGC59) (8 December 1994)

1. In response to your enquiry regarding the ethical, regulatory and economic implications of human genetical research, The British Psychological Society would like to make a number of points:

(i) Whilst the research into mapping the human genome has been well funded and is of high scientific standing, research examining the potential implications (social, ethical, psychological) of this information have not received equal attention. Hence, there is a danger of producing a potentially powerful body of knowledge affecting all aspects of our lives without a proper understanding of its effect on all levels of society. Given the speed at which advances are being made in mapping the human genome, it is essential that more funds are provided to enable the implications of this knowledge to be fully explored.

(ii) There is a lack of understanding of the benefits which may accrue from this knowledge. Whilst certain specific genetic conditions may be cured, knowledge of the human genome is not the panacea for all society's ills as it is often presented. Mapping the genome will not result in beneficial changes in people's behaviour or in society in general, since these are a result of an interaction between genetics and the environment. Mapping the human genome provides information on only one half of the equation. A concerted effort is needed to educate the public on what knowledge of the human genome means for them. This information will overcome some of their fears but also make them aware of potential abuses and limitations of this research.

[1] Council of Europe, Draft Convention for the Protection of Human rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Bioethics Convention, July 1994.

(iii) Mapping of the human genome will eventually enable the genetic constitution of individuals to be known. This has a number of social, ethical and medical implications, very few of which have been adequately studied to understand their impact.

Identification of individuals carrying particular genes resulting in an abnormality may undergo stress themselves without appropriate support structure. The reaction of society, colleagues, employers may change if this information is available. More generally, if examination of an individual's genome become the norm it may result in a genetic underclass of individuals who, because of the presence of particular genes (not necessarily resulting in a clinical condition), may find difficulty in obtaining jobs, insurance, etc.

Ethically it has to be determined who has the right to this information and what are the individual's options once this is available. Can an individual opt to change some of their genes? Can parents choose the genetic make-up of their children? If available, who has the right to request information on the genetic make-up of any particular individual? A major ethical concern must be the potential effect for changing the genetic make-up of the human species. Whilst there are obvious reasons for examining and altering genes that result in adverse conditions, it may not be beneficial that genes resulting in normal variation, e.g., eye colour, be altered.

Medically, mapping the human genome will present opportunities for the treatment of genetic disorders. Potentially, it may also enable other conditions to be treated, e.g., where particular genes predispose the individual, or make that individual more likely to become ill if certain environmental conditions are present. One potential problem may be in the use of information about an individual's genes to determine other medical treatment. Already some medical treatments are "refused" because of the patient's legal behaviour, e.g., smoking and heart transplants. Medical treatment may also be influenced by genetic make-up of an individual.

(iv) There is a clear need for all research into, and applications of, the human genome to be monitored and regulated at local and national levels. Because of the psychological implications of knowledge regarding the human genome, it is essential psychologists are represented at these levels. The application of this knowledge needs careful regulation to prevent potential abuses. This needs national guidelines for both screening and application. Regarding treatment, each case should be treated on an individual level.

(v) The results of mapping the human genome project should become public property and not remain the property of an individual or company.

We hope these comments assist the Committee in its deliberations. Should you require any further information, we would be happy to be at the Committee's disposal.

Memorandum from Dr E Cook, Director of The Whitefield Institute (HGC60) (December 1994)

In response to the Committee's kind invitation to respond to the key issues and questions posed by human genetic research in terms of the ethical, regulatory and economic implications, I shall seek to set out evidence in the terms set by the Committee.

1. General ethical and regulatory issues

1.1 *The Committee asks what do we need to know about the way the genes work in order to make decisions about the use or regulation of genetic information? Are we likely to obtain that information?*

The danger is that the framing of the question itself begs a number of questions. If taken at face value it would seem to imply that we simply gather the information, understand what it teaches, i.e., about the way genes work, and then we are able to decide about the use or regulation of such genetic information. This might well lead to a situation of seeking to close the stable door after the horse has bolted. We may gather information and then find that the implications are so severe that we would rather have tried to regulate before we gathered all the information. The excellent work of the Nuffield Council on Bioethics has shown that it is possible to foresee many of the implications of genetic information and knowledge even before all of that information is in place. This raises a crucial moral, social and political issue of strategy. Do we simply await scientific advance and then seek to respond to the implications of such knowledge? There is an alternative to reactive regulation and legislation. It is perfectly possible to be proactive in relation to the highly likely and even the remotely possible elements of genetic advance. With clear understanding about the current and likely future developments in genetic information, possible genetic manipulation and replacement, it is possible to frame proactive regulatory bodies and standards. This creates a framework of safety for society, a sound context in which genetic research may properly proceed and retain flexibility over the acquisition and application of new genetic knowledge.

What does need to be discovered is the extent to which human genes "cause" disease and how many diseases are genetic or partially genetic in origin and development. It is clear from current genetic research that it is possible to identify particular genes which are directly and inevitably causative in the onset of certain diseases.

These are usually hereditary and considered handicapping. In contrast there are other genetic links which play some role in the development of disease. These are multifactorial diseases and it is often unclear the extent to which environment and experience play a modifying or overriding role or the balance between the genetic and other causes.

We need better understanding of the somatic cell and germ line cell functioning and how both might be modified. Part of this will include a better understanding of the way mutations develop naturally or can be developed artificially and how some genetic carriers pass on the disease without themselves suffering from it. It is vital to have a better understanding of what leads to genetic differences between people and the relationship between our genetic make-up and our behaviour and environment.

Part of a proper concern for the Committee should focus on what counts as "normal" in terms of human genetics. Part of society's unease with handicap and disability rests on some notion of what counts as "normal". This is often quite arbitrary and culturally relative, but may have some crucial root definition and content which relates to what is fundamentally human. It is no accident that certain scientific work has evoked the so called "yuck" factor. That seems to point to some deep fundamental set of values which come into play when a line is crossed, whether that be in the kind of violence involved in the Bulger case or in the use of foetal eggs in fertility work. A clear definition of what it means to be human and what constitutes "normality" will also offer some important insights into the role that medicine should play in the diagnosis of what is counted as "disease" and the nature and extent of "treatments" for such "diseases".

In responding to the question of the likelihood of obtaining this information, it is vital to recognise that knowledge is not neutral or value free. Scientists bring to and express in their own certain core values which affect all they do and the ways in which they transmit the information they obtain. It is possible for scientists to retain such knowledge within the relatively closed scientific community. While for scientific knowledge to be recognised and evaluated there must be publication and validation of theories, hypotheses and new discoveries, there are some who feel that there is an informal agreement among some scientists working on the frontiers of genetics to withhold some information until the social and political climate is more favourable and accepting. While it is impossible to substantiate such fears, it is a cause for concern that there is such a strong focus on public information in a "drip feed" style to encourage acceptance of genetic work. The specific agenda and values of scientific groups needs to be open to public scrutiny and assessment. Without the scientists' good will it will be impossible to obtain the necessary information about human genetics. Knowledge is power and the giving or withholding of information may provide an opportunity for the exercise of power in particular directions. Those who are developing such knowledge are themselves those who will have the most to gain and to lose from various forms of regulation. It is in their best interest to avoid any overreaction or downright rejection of areas of research. This comes sharply into focus as the financial and commercial benefits of genetic information and its control become increasingly obvious. It is no accident that groups within the United States are in favour of patenting genetic discovery and information. This will allow not simply control of that information, but of how, when and whether any associated disease may be treated if some treatment is likewise developed. The global aspects of such scenarios are a cause for concern in the same ways as the development of atomic weaponry or biological and chemical warfare may take place in settings where there are no international regulations or an inability on the part of any such regulatory bodies to control the practice and application of science, including genetic science.

1.2 *Are the current policies being pursued by the MRC and other research funding bodies with regard to ethical and social consequences of research in human genetics adequate?*

For many research funding bodies it is by no means clear that they have responsibility for considering the ethical and social consequences of the research they fund or, more significantly, that they see themselves as having any such responsibility. It is difficult to see how any governmental regulation could or should require funding bodies to accept such responsibility. It is to be hoped that such funding bodies would themselves recognise that such ethical and social responsibility should be part and parcel of a wise stewardship of the funds they have been given. It is, however, perfectly appropriate for government to set universal limits in light of ethical and social concerns. It is also proper for government to encourage such funding bodies to ensure that their membership includes those best qualified to guide on such ethical and social concerns and consequences. The committee should explore the current policies and practice of research funding bodies and ensure that ethical and social concerns do play a part in such decision-making. If not, it should encourage such moves and, if necessary, frame regulations to produce such a result.

1.3 *Has society a right to declare that some research topics should be prohibited because they are intrinsically likely to lead to insuperable moral problems? Should geneticists think more widely than their immediate research goals and their likely consequences or should they leave that to others? Are they pursuing hidden agendas of which the public is unaware?*

Informally geneticists in the UK themselves have drawn a line between research which is on somatic cell work and at this point resisted work on germ line therapy. The main factor in this line-drawing exercise has been fear of unknown consequences. This is partly based on the fact that geneticists, particularly in medicine, have focused rightly on looking for the links between genes and disease or harm. They have not been

investigating the positive values so called genetic "abnormalities" might have. It would thus be tragic if they removed a genetic strain in the germ line, only to discover that humanity had thus lost some fundamental benefit. It is not in itself sufficient to leave such self-limitation to the good will of scientists. The problem is how to draw lines without being perceived to be trying to prevent discovery and innovation or even actually trying to prevent science developing.

In a community, those who are supported and funded by the community must act in service of the community. The very selection of areas of research is part of the community requiring those it funds to act on its behalf using their skills to bring benefits to society. That must also involve ensuring, as far as possible, that harm to society is avoided.

Those in public life and publicly funded scientists may properly be required to uphold the values and limitations set by society. In that sense there is a duty and responsibility on the part of geneticists, those who fund them and public regulatory bodies to ensure that appropriate limits are set.

The problem is that the field of genetics is not yet able to assure society that the crossing of such boundaries as the forbidding of germ line therapy would be controllable or lead to positive good and no harm. It is a catch 22 situation. One way forward may be to encourage concentration on areas which can be developed without foreseeable risk instead of pushing at lines which may carry serious risk. It is important to stress that it is a possibility rather than a conclusive reality. Such a decision if made at the present time would in no way preclude the reversing or adapting of that in different circumstances, where the knowledge base was more secure and the scientific safeguards more secure.

Society and its representatives have a responsibility to protect it and, particularly, vulnerable members of society who would be at most risk from the pursuing of certain areas of genetic research. Laws forbidding economic surrogacy, limiting experimentation on embryos and forbidding the use of foetal eggs in the treatment of infertility are clear examples and precedents for such prohibitions.

While it is all too easy to say that geneticists should think more widely than they do, this needs to be set in the actual context of what is happening. Geneticists are all too familiar with and concerned about the risks to humanity from the wrong kind of developments of genetic understanding and discovery. They are also deeply aware of their own limitations in ethical thought and reflection. It is unreasonable to ask that they become ethical and social experts. It is not unreasonable, however, to expect them to set clear ethical guidelines which are publicly scrutinised and acknowledged. It is also reasonable to expect that they will seek to utilise the expertise of those who are more familiar with ethical reflection. My own experience is that both in terms of the moral seriousness of most geneticists as regards their own work and their willingness to consult and involve ethicists and others in helping them think through the ethical limits and implications of their work. Nevertheless, it is vital that they be encouraged both in their own practice, but also in their formal education and training to develop ethical and research ethics courses and inputs to training and development. They need to be aware that what they discover has far reaching moral and social implications for the rest of society and the world and it may not be easy to prevent genetic knowledge being misused and abused by others. Part of such training and supervision must examine issues of the funding of research, the pressures to "publish or perish", the ambition to become a leader in a particular area of science and the peer group pressure which develops in any academic setting.

The involvement of others, e.g., ethicists, also raises problems of how well informed they are about the actual science and its problems as well as the degree to which they are any more or less objective in their moral advice and reflection. This is an argument in favour of a wide base for such input and regular checking of the validity of such advice as well as giving the appropriate training to enable sound judgments to be made which do justice both to genetic science and ethics.

The role of public opinion is a concern here. Science must not run too far ahead of what society will allow and tolerate. On the other hand science produces new information and possibilities which society often welcomes. Science also produces new kinds of moral dilemmas and society needs to be able to cope with these. Public opinion is a rough and ready means of drawing lines. It is extremely fickle and very much the victim of the information it is given. There will be a world of difference between policies publicly accepted because of horror headlines in the tabloids from those engendered by scientific pressure and publicity.

The role of educating the public about the nature and extent of human genetics and the significance of that information for individuals and society must not lie in the hands of geneticists or scientists alone.

The fear is that some scientists may be pursuing an agenda of their own which revolves round making genetic information and certain genetic manipulation or replacement publicly acceptable. Such an agenda, even if it is difficult to ascertain what it is and how it is operating, must be set in the public arena. The control of information and of medical advances must not lie in the hands of the few.

1.4 *Does research into human genetics lead to a deterministic or any other particular view of human behaviour? Will people try to improve the world through genetic interventions? Should they?*

When it was announced that a team in California had isolated a genetic "cause" for homosexuality, the response showed that society not only believed that this was the case but that anyone carrying such a gene would inevitably become an homosexual. Society also seemed to indicate that if it were possible to screen a pregnancy for such a gene, then a termination would be appropriate. Gay pressure groups expressed deep concern that most people would seek to abort a foetus carrying the "homosexual" gene.

Such examples seem to indicate that the public does regard genetics as being fundamentally deterministic and inevitable. This is usually coupled with a claim that an individual is thus no longer responsible for his or her behaviour. They are simply "victims" of a genetic predisposition. Such a view, if correct, would undermine not only our practice of punishment but also our views of each other and the responsibilities we have for ourselves and for others. It would point towards a society which could be "controlled" by those who were able to manipulate or replace our genetic make up.

Claims about the links between alcoholism and genetics as well as the possibility of such a link with other compulsive addictions do raise fundamental moral issues. The extent to which an individual can be expected to control his or her behaviour is crucial knowledge for how we educate, socialise, reward and punish people and defining reasonable duties and responsibilities for members of societies and of society itself.

Philosophically and theologically it is possible and necessary to resist what is known as "hard determinism". This is quite different from "soft determinism" which recognises that we are limited by our physical and psychological make up and by our experiences in and of life. But we do not live in a closed world where there is no freedom. The presence of indeterminacy in the very nature of reality seems to support such a view. So also does a view of human beings as free and responsible. We are able to make choices and be responsible to ourselves, each other and, for theists, to God for what we do with what we are and have been given.

The role of genetics in determining our human nature, experience and health or otherwise seems to include both an element of necessity—if you have this gene you will inevitably develop this disease—and of freedom—if you have this gene then you need to exercise care in your life style and thus may avoid the conditions which would allow this genetic predisposition to develop. The key role of environmental factors in diseases like coronary heart, diabetes, arthritis, some psychiatric disorders must not be underestimated. The balance between genetic and environmental causation requires further scientific as well as philosophical and theological reflection.

Even if we were sure that there was an inevitable link between having a particular gene and developing a certain disease, that would not prescribe how we should react and treat those who were carriers. Nor should such links distract society from a careful and thorough examination of the role of environment, life style and experience of life in the development of disease and the conditions which lead to disease. The Black Report on Inequalities in Health clearly established the link between disease and social and environmental factors.

The threat of genetic determinism is real to the public and influences many countries, like Germany, in the policies and regulation placed on genetic research. Such regulation must be soundly based on actual facts and a proper understanding not just of the science involved but also of the philosophy of science and of human nature which underlie society and science.

In responding to whether or not people will try to improve the world through genetic interventions it is only necessary to point to the widespread acceptance and use of genetic intervention in the areas of agriculture especially in the development of animals, vegetables, fruit and crops. When this is coupled with demands for sex selection, the use of white embryos to avoid discrimination, abortion on offer or even apparently required if a genetic handicap is identified in utero and the storing and use of sperm from Nobel Prize winners, then it is quite clear that eugenics is not a ghostly spectre but a reality.

1.5 *Germ line intervention would affect later generations who cannot give their assent. Are there other objections in principle to it which can go beyond our limited knowledge of what those effects might be? Would this be playing God? What does that mean and would it be wrong?*

The Clothier Committee and the BMA have both concluded that germ line therapy should not yet be attempted. The Human fertilisation and Embryology Authority concurs. The very fact of unanimity is itself a witness to the degree of concern about such a step. In practical terms geneticists exclude pregnant women from their work to avoid this happening by accident. The arguments against seem to rest on issues of safety, unknown long term consequences and the existence of alternative therapies. These are fundamentally practical arguments which, in principle, might be overcome as scientific knowledge and control improves. The danger of passing some "error" to the next generation or removing benefits by the removal of a so called "harmful" gene can in principle be overcome with time and practice.

The issue of consent is of a different moral order. At the heart of scientific research on human beings lies the notion of fully informed, valid consent or its equivalent. Even in the case of experimentation on embryos and aborted foetal material, consent is still required and given. The problem many are concerned with is whether the woman having an abortion is the best person to give such consent. It seems that the presence of humanity, even in a nascent, developing state is sufficient to require formal consent rather than an assumption that experimental work may be done without some system of checks and balances.

The idea that we have some responsibility to future generations is already prevalent in the ecological discussions. We are urged to behave and live responsibly in the here and now to preserve resources and prevent further ecological damage for those who are yet to come—our children's children. Part of such a responsibility must be an assessment of the nature and extent of risk involved. At the present time it seems that the degree of risk outweighs the desire to push back the frontiers of human knowledge in relation to genetics. It does not seem that the end would justify the means at the present time. It must be queried whether such a moral principle is a sufficient reason for proceeding even if it were likely to be practically justified. Some means may in themselves be so wrong or harmful that they should be avoided, even if a good end might appear. To make such a judgement would require clearer information about what would be involved in germ line therapy and how that might and would affect future generations. Proxy decision making is fraught with problems. Trans-generational responsibility is hard enough with generations we know. It is very difficult indeed with generations yet to come.

The notion of "playing God" raises questions of ultimate responsibility and answerability. For Christians, God is the author and creator of life and humanity is answerable and responsible to God for all it does and in every aspect of life. "Playing God" implies the assumption of power over others which is inappropriate. It is obvious that medicine (and politics) do involve the exercise of power over others. The key is that such power if exercised in the context of freely given consent and in the best interests of those on whom it is exercised. Such moral criteria must remain in place in the genetics debate. Is it possible to obtain freely give, informed consent and can we be assured that the work done is in the best interests of the individual himself or herself or of humanity as a whole. Such justification must be expected and given.

The problem is that such genetic work may involve a fundamental interference with our basic human make up and genetic identity. While most of us would wish to be tall dark and handsome, it is doubtful if that is the responsibility of science. Medicine exists to meet needs rather than to fulfil desires and wants.

It is vital that the basic values and ethical framework of working scientists and funding bodies is clear and open to scrutiny. Any reductionism which undercuts the basic value and worth of individuals and of human being must be resisted. It is wrong to diminish humanity and to do harm to others. For the Christian it is wrong to seek to "play God", but it is not easy to draw lines and to know when crucial lines have been crossed.

1.6 *What should the proposed UN Declaration and treaty on the protection of the human genome say?*

Many doubt whether the human genome project in itself raises any new moral dilemmas. It will provide a knowledge base which then may pose specific issues about screening, manipulation and the replacement of genes.

Any Declaration must address

(a) Open access to information.

(b) Emphasis on the motivation of researchers.

(c) The best interests of the individual and society.

(d) Confidentiality.

(e) Consent.

(f) Responsibility for future generations.

(g) Safeguarding the dignity and worth of individuals.

(h) Protection of the vulnerable in society.

(i) Protection for those with disability and handicap.

(j) Moral education for geneticists.

(k) Control of those who seek to bias the presentation of genetic discoveries and information.

(l) Stress on the universal access to genetic discoveries.

(m) Limiting the move to patent genetic discoveries.

(n) The provision of adequate and appropriate counselling for those affected by genetic discoveries.

(o) International safeguards and regulations in the handling and use of genetic information.

(p) International controls over moves to explore germ line experimentation.

(q) Adequate risk assessment in the development of new genetic techniques.

(r) Awareness of the cost and cost-benefit of genetic research in light of other medical, social and economic needs and concerns in the world.

(s) Focusing and applying genetic research to areas of existing need rather than esoteric research.

(t) Awareness of the need to control the impact of genetic information about individuals on insurance, mortgage and employment opportunities.

(u) To ensure adequate accountability for practising geneticists.

2. PUBLIC AWARENESS AND EDUCATION

2.1 *What is the extent of knowledge of and interest in genetics among different sectors of the public? Should steps be made to improve this and, if so, what form should they take?*

Those in the forefront of genetic work have obviously a vested interest in as open and liberal a policy of regulation as possible. They are also those who have and control the knowledge and its imparting to the wider public. Scientists are deeply interested in and concerned about genetic work as a major step forward in the progress of science and something which creates significant moral questions for society.

The public have many misconceptions about genetic research both in terms of what is actually happening and likely to be discovered and the implications of such knowledge and developments. Thus public opinion should be better informed. This task must not be left to scientists on their own. This is partly to avoid any charge of bias and of an hidden agenda driving the communication of such information. It is also to ensure that the social, economic and ethical issues are presented at the same time and are clearly seen as a part and parcel of the consequences and significance of new genetic work, discovery and information.

This is good reason why bodies like Nuffield, the BMA, the MRC and the HFEA must play a careful and balanced role rather than simply becoming pressure groups seeking to impose their agenda and values on society before society is able to make a fully informed and careful assessment of how it wishes to respond and what limits are appropriate to set for genetic research.

In seeking to improve public interest the need for objectivity and clarity is vital. The implications of genetic information are many and various, thus it is vital that the improving of public-awareness must be done in ways which are comprehensible and easily accessible and which carry a clear presentation of the implications, consequences and of the social, economic and moral significance of that knowledge.

This may involve exploring the possibilities of inclusion of genetic strands in the National Curriculum, expansion of the material from the British Association for the Advancement of Science, as well as public debate in the media.

2.2 *Is there a general anxiety and suspicion about research in genetics? Is it justified or should it be allayed and, if so, how?*

There is such suspicion, though its extent needs to be properly established. Scientists are faced with a genuine dilemma. The more they impart information which is not fully understood the greater the reaction is liable to be. It is no accident that after a BBC Radio 4 broadcast of new discoveries in medical research on a Friday morning on the "Today" programme leads directly to people in GP's surgeries in the mid morning asking for the new treatment. They do not realise that such discoveries are likely to have a four or five year lead in before they are freely and generally available. Part of this misunderstanding arises from the media presentation and part from the public's desire to seize on anything which appears to offer hope in settings of disease, pain and distress.

The extent to which such suspicion and anxiety is justified or needs to be allayed may only be assessed in light of the reaction to public announcements like that of the "discovery" of the "homosexual" gene, the moves towards sex selection, public and scientific concern over the implications for the development of new weapons based on biological and genetic discoveries and the present failure to provide adequate counselling and checking of informed consent for those, like pregnant women, who are offered screening for genetic disorders. This suggests that the way forward must address each of these concerns directly and put in place adequate counselling and consent procedures.

2.3 *Are there unreasonable expectations of the benefits that might come from genetics? If so, should these be tempered?*

The very success of science is sufficient to encourage the public to believe that medicine will in the end conquer all disease. The knowledge that massive resources have been invested in a world wide project to map the human genome seems to imply that the benefits will far outweigh the cost and harm. Few realise the speculative nature of scientific work and the hard slog to establish any kind of scientific validity. It may also be that the publicity attendant on the Human Genome Project has led to exaggerated expectations on the part of the general public.

An air of realism needs to be included in all attempts to educate the public and in media programmes dealing with the science of genetics.

2.4 *Is there a danger that genetics will be seen as an excuse for socially unacceptable behaviour? Could it be used to justify reductions in social programmes of health, education and welfare?*

It is always possible to abuse knowledge and to misuse science. The link between behaviour and genetic make up is far from being conclusively and exhaustively proved. The reductionism and determinism implicit in such a view of the world needs to be challenged and refuted. That, however, must not lead to a denial of the

key role of genetics in our state of health and our susceptibility to disease. The possibilities of manipulation and replacement of defective genes should offer a counter argument to a trend to dismiss or even get rid off people who are carriers of "socially unacceptable" genes. This highlights the difficulties of defining what counts as socially acceptable and unacceptable.

It would only be if certain reductionist and deterministic views of life became the basis for public policy making that such information would be used to justify reductions in social programmes. This warns us that basic set of values which underpins scientific, social and public life must be clearly expressed and embraced by the whole of society. Public morality and the scientific and political applications of knowledge must go hand in hand.

2.5 *What are the right questions on the bearing of genetics on human behaviour, ethics and belief?*

(a) To what extent does genetic material predispose or predetermine the development of disease in an individual?

(b) To what extent are we at liberty to change the genetic basis of an individual?

(c) To what extent are we at liberty to change the genetic basis of humanity?

(d) What are the implications of any such genetic link with disease for insurance, mortgage, employment and screening arising from genetic discoveries?

(e) What are the possibilities of abuse and discrimination arising from screening programmes, if a genetic link is clearly established?

(f) How should confidentiality be safeguarded in genetic work, if it is clear that there is a significant link between genetic material and behaviour?

(g) How should fully informed, valid consent be obtained in genetic experimentation, if there is significant risk or possible harm for an individual in knowing the results of such work?

(h) What limits should society set on genetic research in order to protect the vulnerable in society?

(i) If it is established that an individual is a carrier of a handicapping or disabling gene should that automatically lead to abortion?

(j) What limits should we set to experimental work which might affect the behaviour of future generations?

(k) What values should be expressed and required in genetic research and funding as well as in the communication to the public of genetic information and creating of regulatory controls on genetic work?

(l) To what extent are human beings free and what structures of responsibility are necessary for the well being and survival of society?

(m) To what extent are animal models and experimentation useful and morally acceptable in genetic research?

(n) What are the possibilities of developing new forms of weaponry based on genetic research? How may this be avoided or controlled?

3. Genetic disease

3.2 *Are there any ethical questions about somatic gene therapy which are different from other types of therapy which affect only the patient receiving them?*

There is general agreement that there is, in principle no new type of ethical dilemma posed by somatic cell gene therapy. Nevertheless, it must be stressed that the fundamental nature of the material involved concerning human identity and being raises psychological, religious and ethical questions about the handling of the very stuff of life. Part of the problem is that genetic research begs many questions about the definitions of "normality", "abnormality", disease and cure. As already indicated issues of discrimination, justice, protection of the vulnerable, abortion, needs versus wants, enhancement of individuals and their characteristics, the impact on family life, insurance companies, mortgage, employment, screening, eugenics, confidentiality, consent, counselling services, communication, regulation of research and research funding and the implications for the economic and social well being of society together frame a concatenation of problems which seem unique. No haphazard, piecemeal approach will be sufficient to deal with the cluster of issues for they are interdependent and require some coherent and co-ordinated response.

3.3 *Should information about an individual's genome be regarded as confidential or should it be possible for employers, insurance companies etc., to require genetics tests or to obtain the results of previous tests on an individual or their relatives? If not, why is genetic testing any different from current medical tests?*

At the heart of modern medial practice lies the autonomy of the individual and the need for confidentially. This is both for the benefit and protection of doctors as well as patients. When insurance companies, employers and the like ask for private information to be made available to them, it is only proper for that to happen when and if a patient has given specific consent. It is part of the doctor's responsibility to ensure that the patient

understands the significance of that information and what might follow from it being made available to others. When it comes to information about genetic make up the individual may have little or no control over how that make up will affect him or her. With some genes there is an inevitability about the results, with others a variety of environmental and experimental factors will and no doubt affect the onset of any disease. It is virtually impossible for an individual to be aware of all the possible implications of his or her behaviour in relation to his or her genetic make up. Indeed there may even be contrary effects from the same action so that avoiding the onset of one genetically based disease may lead to the greater likelihood of developing another.

The growth of genetic information is likely to reach such enormous proportions that it will be almost impossible for employers and insurance companies to assess the risk and likelihood elements and to balance these. This, however, will not prevent such groups seeking to gain such information. To allow them to set specific genetic tests before offering insurance or employment will inevitably mean discrimination and the creation of a permanently unemployable and uninsurable group of people in society. This may mean that the rest of society will have to pay higher premiums in order to protect the few who are at risk.

There are some who argue that insurance companies will not begin to screen clients because there are too many tests which will become available and the sheer cost of such testing would in itself be prohibitive. Insurance companies lack the counselling resources and expertise to make such testing properly and ethically sound.

If, however, that information is already available in the normal practice of asking for a family history it is unreasonable to seek to remove that information from the public record. In the work setting it is only when a particular disease might pose a risk to the individual himself or herself or to others in the work place that specific testing should be permitted. This is illustrated when testing for HIV and Aids became advised by HIV and AIDS support groups after a long history of resistance to such tests on the ground of discrimination. When it became evident that there were genuine benefits to the individual in knowing his or her HIV status, their recommendation changed.

3.4 *When is population screening for genetic disease appropriate? What factors, such as cost and the availability of counselling and treatment, should be taken into account? How should screening be organised and regulated?*

Any decision to screen the population depends on the availability of such reliable testing, adequate counselling and treatment options being available and such a step being cost effective. It is in the realm of pregnancy screening that experience has shown problems with false negative and false positive results, the choices exercised by potential parents in terms of abortion or of seeking artificial fertility treatment measures, concern over the level and adequacy of information given, adequate consent being sought and safeguarded and the problem of identifying a disease even when there is no possibility of a cure. Some wish to know in advance of developing a disease or of having an handicapped child, while others are frightened by such knowledge and feel unable to cope with the implications.

Examples of good and bad screening programmes stem mostly from the United States where programmes designed to screen for Sickle Cell Anaemia and Tay Sachs disease have raised questions about discrimination, confidentially, consent and counselling.

Any programme of national screening should only take place where treatment is available, or a positive test will give people adequate and reliable information on which to base life changing decisions affecting themselves, their children and their families.

3.5 *If screening for a wide range of genetic predispositions becomes routine, how will people be protected from discrimination on the grounds of their genotype? Should they be?*

Strict regulation, ensuring adequate consent and confidentiality as well as legislating to outlaw discriminatory practices would be the kind of steps necessary to protect the vulnerable. The implications for people with disability or handicap are enormous and this would put an increased strain on our national resources and responsibility for the disadvantaged in society.

3.6 *Would people be well advised to seek genetic information from sexual partners before the conception of children? Are they likely to? Is this likely to change with future research?*

In a society where sexual intercourse and the having of children seems to be increasingly casual rather than carefully considered, it seems extremely unlikely that people will move in such a direction. The level of honesty concerning an individual's HIV status should have made people aware of the risks of sexual intercourse outside the confines of a faithful, exclusive monogamous relationship.

It is already the case that blood tests are a requirement before marriage in many of the United States, so it is possible to legislate as well as to encourage people to seek such information. Such a step would change the current perceptions of relationships which are based on mutual selection and attraction rather than a cold blooded calculation of the risks and benefits in childbearing and rearing or the likely level of dependency if some known disease were to develop. There are some who would seek such information, but it would add a formal and less

than romantic aspect to relationships. It might also avoid a great deal of pain for all those involved and likely to be affected.

6. Evolution

Some public concerns reflect unease about the possible effect of genetic interventions on the long-term future of the human race.

In dealing with the various questions in this section it is important to avoid any deterministic view of evolution as a necessary, closed and inevitable process. The main difference being contemplated is rather than allowing natural processes to develop, human being will increasingly direct and control the process of evolving human beings in terms of both specific and general characteristics. While such control of change may already be happening, it is very far from the scale of possible interventions made available because of genetic information and understanding. Such possibilities should drive us back to asking fundamental questions about the nature of human being, identity and society. It should also raise questions about the basic values which underlie social and scientific work. These must include the protection of the individual and his or her dignity, worth and value, the use of medical and scientific knowledge and expertise for the benefit and well being of individuals and humanity as a whole, a maintaining of standards of truth, justice, integrity, and a concern on the part of society as a whole for those who are vulnerable to discrimination, abuse or destruction.

From a Christian perspective all of life is to be seen in relation to God and his standards. In a "post-Christian" society, these values remain crucial for the well being of society. I believe it is possible to describe and agree on such essential principles and values and that the enunciation of them is vital in all scientific, public and political decision making relevant to the development of the human genome project.

Memorandum from SmithKline Beecham Pharmaceuticals (HGC64) (12 December 1994)

Genetic screening outside of "serious disease"

1. The prospect of the extension of genetic screening beyond serious disease encompasses:
   (a) Commoner medical conditions.
   (b) "Normal human traits" not usually considered as associated with disease, including a spectrum of behavioural traits not defined or characterised as a disease state. Also included in this group are traits associated with the normal range of intellectual and physical performance, and appearance.

As the business of SmithKline Beecham covers disease management, most of the comments will be confined to the issues involved in extending genetic screening beyond serious disease to broader medical conditions.

Previous attempts to define "serious disease" have been controversial. The limits set by the Clothier report on gene therapy are too narrow and would be inappropriate to guide genetic screening where the safety considerations and benefit risk balance are quite different.

There is no reason to suppose that genetic screening should be confined to the most serious diseases. It is usually considered that genetic screening does not create unique issues. While it is necessary to recognise that genetic screening may have greater family implications or confer a greater sense of certainty by comparison with other forms of diagnosis, these issues do not detract from the principle that genetic screening should be subject to the same considerations as any other diagnostic approach.

Thus, commitment to disease diagnosis is not often qualified by a seriousness threshold. In short, the criteria for the introduction of genetic screening, irrespective of the "seriousness" of a medical condition should be the same as for any other medical screening procedure and should be based on:

- Accuracy and quality control of the diagnostic procedure.
- Availability of counselling/medical advice.
- Cost-effectiveness.

2. We do not agree that the best solution would be to assign to a central co-ordinating body the responsibility for distinguishing between serious disease and other medical conditions for the purpose of deciding on genetic screening (Nuffield report, 10.3). As the Nuffield report discusses (3.10), the perception of seriousness will vary between societies and according to treatment possibilities. The issue of classifying disease severity for genetic screening is the same as the issue of deciding other healthcare priorities and should be approached in the same way (presupposing the existence of a validated screen and agreed diagnostic criteria). That is, presently, either

by explicit, comprehensive priority-setting of all healthcare services or by consultation within the individual doctor-patient relationship.

3. Genetic screening should only be performed with the objective of the betterment of human health and with informed consent. Genetic screening should benefit the subject in the sense that the interests of other constituencies who might benefit (including family members, insurers, employers)—while often legitimate—are not adequate to support the imposition of testing. By analogy with certain immunisation strategies, however (where the prime purpose is community rather than individual protection), the issue of "community health products"—the potential to develop cost-effective genetic screening for community benefit—requires further discussion.

4. The value of genetic screening for any disease is decided by considerations of benefit:risk (potential good outweighing possible harm). Genetic screening for medical conditions outside of "serious disease" may well have a more favourable benefit:risk balance than screening for those serious diseases where no current treatment is available (e.g., Huntingtons disease).

5. The extension of genetic screening from serious disease to other medical conditions does not raise new ethical or social issues but increasing the scope and scale of screening may accentuate some practical problems. For example, there is an ever-increasing need to resolve issues associated with the potential for economic stigma (insurance and employment implications) and with quality control of testing and counselling. Arguments against genetic testing based on economic stigmata, quality testing and quality counselling are arguments for addressing these other issues rather than prohibiting testing.

6. Because of the complexity of the genetic basis of some of the medical conditions (multiple gene and environmental influences) whether or not classified as "serious", e.g., obesity, depression, schizophrenia, alcoholism, genetic prediction is likely to be probabilistic rather than deterministic. In these circumstances, genetic information is important if it allows the individual to consider changes in lifestyle and participate in research to understand the pathogenesis of the disorder and, hence, develop better therapies. Such patients will be offered novel disease-modifying treatments at the earliest opportunity. Accuracy in communicating the true meaning of a genetic test result to the patient, including non-directive genetic counselling, is essential for all genetic testing.

7. Going beyond current definitions of disease, the possibility of screening for "normal" states associated with behavioural traits, perceived by society as damaging, is more contentious. Genetic testing will identify a new spectrum of disease: behavioural traits which will prove to have a clear pathogenic basis. One recent example, illustrating many of the issues, is aggression. Would a pathogenetic explanation (in terms of monoamine oxidase A activity) be helpful in removing the stigma associated with individual/family fault-finding and, ultimately, in identifying dietary or pharmacological interventions to limit aggression? Or, would screening bring new economic stigmata and would prevention of aggression be a net benefit to society (if it also discouraged assertive and entrepreneurial traits)?

8. The recent draft convention on bioethics from the Council of Europe (article 16 paragraph 110 "interventions aimed at modifying genetic characteristics not related to a disease are prohibited") reasonably represents the traditional viewpoint, although it needs to be recognised that nosology is an evolving subject.

The business of SB is healthcare and we agree that extension of screening to normal human traits would be more controversial and is contingent on the definition of normal. Nonetheless, paternalistic recommendations on what society and individuals may reasonably seek must be viewed critically. A recent rationalist view asks that genetic research be judged in a broader context of what people want and what society permits in biological enhancement (Miller, Lancet 1994 *344* 316-7).

9. The development of new genetic screens for disease can be considered pragmatically using utility criteria based on the principles of Wilson and Junger (WHO 1968, discussed by Shickle and Chadwick, J Med Ethics 1994 *20* 19-22):

— The condition should be an important problem:

  Includes high-prevalence conditions as well as serious disease.

  Who decides what is "important"? The key is the patient.

— There should be an acceptable treatment:

  Definitions of adequate treatment should not be restrictive and can cover environmental modifications and provision of professional advice.

— There should be a suitable test:

  In terms of validity and reproducibility.

  Appropriate facilities for diagnosis and treatment should be available.

— Case finding should be cost effective and there must be a sustained commitment to testing.

Application of these criteria to screening in disease provides a mechanism to avoid the arbitrary limitation of "serious".

It is premature to go further, beyond the current notions of disease, for that move must reflect a debate within society at large and will require greater efforts in educating and informing public understanding.

KEY QUESTIONS

1. *What assistance in the treatment of disease or the design of drugs is given by knowledge of the gene(s) associated with a particular disease?*

Knowledge of the gene(s) associated with disease will greatly advance the understanding of pathophysiology, diagnosis and the discovery and development of novel drugs:

- Protein therapeutics.
- Vaccines.
- Small molecular therapeutics (proteins as targets).
- Gene therapy.

We give detail of our views on each of these topics in subsequent answers. In this answer we provide a general overview of the therapeutic opportunities emerging from human genetics research.

Genomics—the study of the genetic control of body function in health and disease—has profound implications for life sciences R&D. Indeed, a recent Office of Science and Technology Working Group on the UK Human Genome Mapping Project predicted that increased knowledge of basic biology within genomics will eventually transform medical practice.

Genetic information will aid our understanding of the disease processes underlying single gene disorders and of the genetic components of common multifactorial diseases (e.g., cardiovascular diseases, cancer, asthma, autoimmune diseases, psychiatric disorders). This increased understanding will stimulate the development of novel diagnostic agents for detection and for testing predisposition, and the development of novel therapeutic and preventive agents. There will be accelerating progress towards the identification of curative rather than symptom-relieving drugs.

In the past decade, the critical roles of protein science and biotechnology in the drug discovery process were institutionalised within the major pharmaceutical companies. For SmithKline Beecham, capitalisation on these advances led to the introduction of pioneering biopharmaceuticals (e.g., the thrombolytic agent, Emainase, and the hepatitis vaccine, Engerix B), and to an increasing appreciation of the importance of characterising proteins as molecular targets for discovery research. The recent advances in genomic technologies will enable faster identification of potential molecular targets, the cornerstone of new drug discovery efforts. Thus, the traditional and laborious identification of the gene corresponding to a culprit protein in a diseased tissue has been replaced by the sequencing and expressing of target genes following the identification of expressed sequence tags (ESTs) in cDNA libraries prepared from diseased tissue.

New leads in discovery research are emerging for a number of diseases, ranging from newly revealed receptor subtypes, isoenzymes and membrane ion transport systems to novel classes of biopharmaceutical proteins with therapeutic potential in their own right. These advances in understanding of the molecular basis of disease are expected to facilitate the search for pioneer low molecular weight therapeutics as well as inspire new avenues of intervention (gene therapy, antisense technologies, therapeutic vaccines).

In addition to the impact on drug discovery research, genomic technologies will also expedite many aspects of drug development. For example, in safety evaluation, preclinical assessment of drug metabolism by subclasses of human P450 enzymes will be possible. In clinical efficacy trials, genomics provides an increasingly sensitive tool to devise a novel framework for specific diagnosis, selective therapy and prediction of non-responders. Genostratification of patients as an entry criterion in clinical trials will allow more efficient interpretation of pharmacoeconomic value, as well as therapeutic efficacy. There is also the prospect of learning more the relationships between pharmacokinetics and pharmacodynamics, in terms of resultant gene expression in the target tissue or the identification of an appropriate surrogate endpoint.

In consequence of these advances in genetic medicine, it is likely that medical practice will be better able to predict and prevent disease. This change could help to meet the Department of Health "Health of the Nation" targets—focusing on prevention as much as on cure. Diagnostic technology will, increasingly, be brought into the primary care sector—assuming that the appropriate access, use and location of diagnostic facilities will be forthcoming from NHS policy research (identified as a high priority in the 1994 Report to the NHS Central R&D committee "R&D Priorities in Relation to the Interface Between Primary and Secondary Care"). Advances in diagnosis will drive lifestyle changes and there will be increased opportunities for self-diagnosis.

Gene therapy will introduce genes into cells to replace functions lost through mutation or other processes or to induce production of proteins not normally expressed in the tissue. Gene therapy represents only one—and

in the near term, perhaps a minor one—of the new product categories that will become available from genomics research; there will also be many new opportunities to develop small molecular weight drugs (New Chemical Entities) and protein therapeutics.

2. *Are there differences, in principle or in practice, between gene and conventional therapy? How might these affect development costs? How will this affect the actual cost of treatment?*

We want to take this opportunity to emphasise, as described in the answer to the preceding question, that gene therapy is by no means the only or even the primary therapeutic development that will emerge from genomics research. Genetic information will also increasingly be used in the discovery of small molecular therapeutics, protein therapeutics and vaccines. Subsequent answers will exemplify some of SB's activities in these areas.

Gene therapy, conceptually, incorporates elements from drug therapy, vaccination and transplantation. Gene therapy is eventually likely to be available for a variety of disorders not just those traditionally recognised as monogenic. This wide application of somatic gene therapy to common diseases was highlighted at the recent UNESCO International Bioethics Committee meeting. For example, discussion took place on the genetic engineering of cells to provide protection against HIV or the side-effects of cancer treatments (Nature 29 September 1994, p369).

The commercialisation of gene therapy is under strategic evaluation at SmithKline Beecham and we believe it is too early to consider in detail what the costs of development might be. The science is relatively new and much remains to be established before it can be applied in practice (e.g., optimising vector technology). Nonetheless, we suggest that the R&D issues are similar in principle to those pertaining in other areas of (bio)pharmaceutical R&D, in terms of the need to establish quality control, demonstrate safety and efficacy and define value in terms of risks and benefits to the individual.

As for any other medicine, the cost of treatment cannot be considered in isolation from other healthcare costs nor should cost be considered in isolation from benefit. The potential of somatic gene therapy to address presently-unmet medical needs, and to intervene in disease pathogenesis rather than provide symptomatic relief, may be powerful influences in containing total healthcare costs. For example, if new advances permit better prediction and prevention in oncology, there will be, not only major patient benefits, but also dramatic decreases in NHS costs (e.g., through lower demand for surgery, radiotherapy and other hospital services).

3. *To what extent do factors, such as technology-transfer facilities, patent protection and regulation, influence the commercial exploitation of research findings?*

Regulation

National advisory committees on gene therapy provide a forum to discuss issues. This type of discussion appears to be valuable in encouraging innovation during the early days of gene therapy R&D. As the technique becomes routine, regulation should be provided by the same procedures as are applied to any other medicine development ("it will be no more dangerous than any other therapy, and should be regulated in the same way", UNESCO International Bioethics Committee).

With regard to other regulations, there are dangers that overregulation of the use of biotechnology and genetics research as enabling tools—particularly in response to European Union initiatives—will damage UK competitiveness. These dangers have been recognised in the House of Lords Select Committee Report (1993) on Regulation and Biotechnology Industry and acknowledged in the recent Government response to that report. Rather than relying on processes of overregulation to stifle public qualms about new technology, it is far preferable to raise public confidence by instilling a better understanding of what science is doing.

Patents

Numerous human genes isolated by recombinant DAN technology have already been patented, allowing successful commercialisation of life-saving medicines. Prominent examples include plasminogen activator, the interferons, human insulin, growth hormone and the colony-stimulating factors. Our approach to patents in genetic medicine is that we aim to satisfy the same patentability criteria as required for any other invention which, generally, are: novelty, non-obviousness and industrial applicability. Thus, we wish to patent those sequences which, on the one hand, meet the criteria for patentability and, on the other hand, have the objective of improving human health.

Healthcare companies cannot commit the large resources needed for novel drug R&D without patent protection of their Intellectual Property Rights. We recognise that there are those who believe that a full consideration of ethical issues should be the responsibility of the national patent offices. This view was also recently espoused by the House of Lords Select Committee on the European Communities ("Patent Protection for Biotechnological Inventions" 1994). We reject this view, recommending instead that ethical issues should

continue to be matters for society as a whole, and Parliament and Government in particular to consider and determine.

We are particularly concerned that the proposed EU Directive on Biotechnology, currently under consideration in the Conciliation Committee of Parliament and Council, should properly establish and codify intellectual property rights for products and services derived from biotechnology.

Technology-transfer

Our specific experience in genomics research is described in more detail in the answer to question 5. General aspects of our liaisons with academia were discussed in the evidence we presented to the earlier enquiry of this committee ("The Routes through which the Science Base is Translated into Innovative and Competitive Technology" 1994 Volume II pp 133–148). We value the many individual relationships in the UK that help us to participate in frontier research and access new technologies and tools. By comparison with the US, however, we still see that the UK is characterised by a relatively stark divide between academia and industry. We fully endorse the point made by the Chancellor of the Duchy of Lancaster in the debate on Scientific Research on 2 February 1994, concerning the increasing cultural separation between academic science and "wealth creation" science. Furthermore, in the USA technology-transfer is often catalysed by the SME sector and the UK is at a competitive disadvantage as regards the number and diversity of venture capital, start-up companies. UK national competitiveness may improve in consequence of the recent changes in requirements for listing such companies on the London Stock Market.

4. *How does the regulatory regime for genetic-based industry in the UK compare with that in other countries? Is there a danger that investment will be lost to other countries with different regulations or with better venture capital funding potential?*

As a UK-based multinational company, SmithKline Beecham seeks to integrate its R&D worldwide to capitalise on the availability of ideas and tools wherever they maybe found and whatever their antecedents. Some of our concerns on the UK climate for innovation were introduced in the preceding answer. We are particularly concerned at progress on the directive on biotechnology patents within the European Union, and at the inappropriate process which resulted in unacceptable amendments. At present, the outcome is in doubt and we are alarmed that we may lose the ability to patent the fruits of our genomic research even though our inventions satisfy the customary patentability criteria.

We make some other general points about the UK science base in our answer to question 6, but we would like to emphasise one point here. SmithKline Beecham is a healthcare company—biotechnology and human genomics research are simply enabling technologies that we expect to use in R&D of novel medicines and services. The competitiveness that matters to us, is in healthcare, and in this context, we remain concerned about UK government initiatives, new pricing constraints, and other advice (e.g., House of Commons Health Committee 1994 "Priority Setting in the NHS: The NHS Drugs Budget") that may damage the environment for innovation. In particular, the proposal that Government should decide what R&D should qualify as relevant to the future priorities of the NHS or that it should decide after five years experience what medicines should remain available within the NHS, would constitute a bureaucratic interference with medical science which would run counter to the development of new technologies and medicines for the relief of disease.

5. *What is the involvement of your company in genetic research? Have you any products currently in development based on such research? Approximately what proportion of products under development does this represent? Do you expect to develop such products in the future? If so, will you do so in house, through collaboration with academics or through acquiring IPR? Do you expect to carry out such activities in Europe, North America or elsewhere? Please indicate if any of your answers to this question is to be treated as commercial in confidence.*

Our current development portfolio includes several genetically engineered vaccines (herpes, Lyme, malaria, influenza). Similarly, every internal discovery programme at SB uses human proteins as targets for drug action, isolated using genetic engineering methods. We have established collaborative arrangements with several new biotechnology companies and the establishment and maintenance of a network of academic collaborations is also a key priority. Products have already entered development as a result of both our internal research and these collaborations, including: soluble complement receptor for ARDS (Adult Respiratory Disease Syndrome), genetically engineered monoclonal antibodies to treat allergic disorders, viral infections and autoimmune diseases such as rheumatoid arthritis. Genomics research is an integral and essential component of all our drug discovery efforts—proteins as targets as well as therapeutics.

In 1993 SmithKline Beecham and Human Genome Sciences (HGS) formed a major strategic alliance to collaborate in large-scale gene sequencing to identify the structure and function of human genes in health and disease. Under the terms of agreement, SmithKline Beecham receives the first right to develop and market

human and animal healthcare products in several significant fields developed from gene sequence data identified by the collaboration. HGS, both through its direct activities and its collaborative relationship with the Institute for Genomic Research (TIGR), represents one of the largest genomic discovery groups in the world. SmithKline Beecham contributes complementary technology to the partnership. We have efficient computer database systems and links via Internet with gene databanks. Furthermore, in our worldwide Biopharmaceuticals R&D organisation, we have state-of-the-art expression capabilities in both microbiological (bacteria and yeast) and animal cell systems. Additionally, we have considerable expertise in small and large-scale protein purification, X-ray crystallography and multi-purpose state-of-the-art pilot plants (including up to GMP standard) for rapid scale-up when required.

Together with HGS we are providing financial support for the largest human gene database in the world. The information and materials that make up the database, called The Human cDNA Database, are the product of the joint research project between TIGR and HGS. The database includes partial and complete DNA sequences characterising between 30,000 and 35,000 human genes; it also provides information about where in the body and how frequently individual genes are expressed. This information includes more than 150,000 partial human gene sequences, substantially more than are available from any other source; in many instances, several gene fragments relate to a single gene. In elucidating the structure of these fragments, the exact sequence of more than 50 million nucleotides was determined. The database will be available to researchers at non-profit institutions who sign access agreements. Those researchers may use the data however they wish, and they may publish their work as they wish, provided they cite their use of the data. Not all the data are proprietary. If, however, those data that are proprietary are used in making a patentable discovery, HGS has an option to license that discovery. If HGS exercises that option, HGS and the inventor's institution would negotiate the terms and conditions of a licence, including royalties payable to the institution. If the option is not exercised, the institution is free to commercialise the discovery without further obligation to HGS. Discoveries available to HGS through its collaboration with the Institute for Genomic Research, flow in turn to SmithKline Beecham under the terms of our collaboration agreement with HGS.

6. *Is the UK a good place to conduct such research?*

In addition to the specific points made in answer to earlier questions we would like to take this opportunity to make some general observations on strengths and weaknesses in the UK science base.

We have two primary requirements of the academic sector: well-trained people and good basic research. We are greatly concerned at the "retreat from science" that has taken place in the UK over the last couple of decades and at the danger of complacency in assuming that the poor exploitation by industry of good academic science is the dominant problem in the UK science base.

Although the UK has great strengths in human genetics and genome analysis, these areas are not immune from the problems have beset the academic science base. For example, DNA sequencing technology is rightly identified as a critical element in the priorities and opportunities described in the OST report on the Human Genome Mapping Project and this was an area in which MRC-sponsored research led the world. This research lead passed to the USA, where the novel sequencing methods are now being developed. In consequence, the UK has lost competitiveness, not just in terms of the commercialisation of the technology (for example sequencing machines) but, much more importantly, also in terms of the immediate opportunities for novel healthcare products.

We suggest that urgent reform is needed in the UK to reverse the passive neglect of the university system, the decline in proportion of students choosing careers in science and the erosion of science teaching in primary and secondary education. Limitations in public understanding and esteem are influencing the environment in which we seek to deliver new products and services.

Government emphasis in the White Paper on S&T, on the use of science base in pursuit of national goals and on developing a shared responsibility between government, industry and academia resonates with our views and is greatly welcome if it signifies the end of the era characterised as the "retreat from science". We are enthusiastic participants in current S&T initiatives, for example the Technology Foresight Programme. However, the solution will be found not just in the prioritisation of resources within academia and an increased commitment to partnership between academia and industry. Successful application of genomics research in the UK also requires a redoubling of effort to educate and inform all stakeholders, starting in primary and secondary education and extending throughout educational processes in support of public understanding on these topics that are surely of the greatest personal interest to us all. For example, reform of the post-16 syllabus, broadening the curriculum to allow all students to study some science, should yield a better informed public-at-large as well as create a large pool of those who might wish to graduate in science. At present, industry, society and young people themselves continue to lose opportunities for profitable, intellectually-challenging and personally-satisfying work to the disadvantage of the UK as a whole.

1. General ethical and regulatory

Preamble

The bioethical dimension of genomics and the Human Genome Project has evoked substantial debate. Although the issues are by no means unique to genetic medicine, their identification has crystallised concerns within various constituencies about the pace and scale of technological change and its implications.

Specific issues range from anxieties on confidentiality and economic discrimination in genetic screening to unease on alterations in genetic inheritance by germ line gene therapy, to debate about the ethics of commercial patenting of the inventions arising from genomics research. However exciting the individual technological advances, it is imperative that the healthcare community formulates the social and ethical policies to ensure that genetic medicine is used for the betterment of human health. We in SB recognise and accept the responsibility to contribute to this discussion and to develop and articulate an ethics policy to guide our healthcare business.

Bioethics policy initiatives are now emerging at a rapid pace from national and international bodies (prominent activity by UNESCO, Council of Europe, European Union). In the UK, the Nuffield Council on Bioethics has done much to inform the current debate on genetic screening. We endorse the following general recommendations that have been made in the UK: Informed consent should be a requirement for all genetic screening programmes. Individuals should be fully informed of the results of genetic screening and in particular of the implications of those results for the family. Health professionals should seek to persuade individuals to allow the disclosure of relevant genetic information to other family members. Genetic screening of employees for increased occupational risk ought only to be contemplated where there is strong evidence on two grounds: a clear connection between the working environment and the development of the condition for which genetic screening can be conducted; where the condition in question is one which seriously endangers the health of the employee or third parties.

1.1 *What do we need to know about the way genes work in order to make decisions about the use or regulation of genetic information? Are we likely to obtain that information?*

The necessary level of knowledge relating both to advances in technology and the emergence of products is a fast-moving target. We share the OST call for urgent attention to be given to the dissemination of information and promotion of understanding at all levels (OST Report 1994 "Priorities and Opportunities in Genome Research"). We also agree that there needs to be urgent assessment of the needs of the major stakeholders for genetics expertise (in Parliament as well as industry, academia and the health services).

As detailed in the answers to previous questions, we are already using the genetic information available to develop novel products. There is certainly no need to wait until completion of the Human Genome Mapping Project before embarking on the decision to progress products and services in healthcare. As emphasised in our previous answers, regulation of the novel therapeutics and diagnostics should be subject to the same procedures as any other therapeutic or diagnostic. Unique regulations are not required just because genetics is employed as an enabling technology.

1.2 *Are the current policies being pursued by the MRC and other research funding bodies with regard to ethical and social consequences of research in human genetics adequate?*

There is considerable academic activity on bioethical issues in genetics research, partly in consequence of the funding provided by the Human Genome Mapping Project. It is our view that these ethical and social issues are, in large part, not unique to genetics, but we agree that genomic advances and claims will heighten the need to address social and ethical concerns about:

- Prenatal and pre-implantation testing.
- Potential screening for, and exclusion from, health and life insurance.
- Genetic selection and discrimination in the workplace.
- Patenting human genes.
- Social stigmatisation and creation of a genetic underclass.

In the UK, these concerns have been highlighted for discussion by the OST (delegating to the Nuffield Council on Bioethics), the Royal College of Physicians and ACOST (Report on Medical Research and Health 1993, identifies uncontrolled and inefficient activities of individual Health District Authorities in screening for genetic disease).

As we stated in our preamble to these answers, we support the thrust of the recommendations made recently in the UK by the Nuffield Council (and in the US by the Institute of Medicine). It is important to ensure that these efforts at the national level take account of other bioethics efforts at a pan-national level: UNESCO, the European Union (Framework Programme 4 studies on biomedical ethics; DG XII Working Group on Ethical, Social and Legal Aspects of Human Genome Analysis: Group of Advisers on the Ethical Implications of

Biotechnology, European Parliament STOA advisory office), Council of Europe (Bioethics Convention), World Medical Association and WHO (with CIOMS). We have worked with the Nuffield Council to provide views for their current enquiry on Genetic Screening Outside of "Serious Disease" (a copy of our evidence to the Nuffield Council is appended to these Q&A).

1.3 *Has society a right to declare that some research topics should be prohibited because they are intrinsically likely to lead to insuperable moral problems? Should geneticists think more widely than their immediate research goals and their likely consequences or should they leave that to others? Are they pursuing hidden agendas of which the public is unaware?*

As emphasised elsewhere, this requires a new commitment to educating and informing all of the population. Society has a right and a duty to discuss the issues. Geneticists, in common with all those personally involved in genetics research (including ethicists) should certainly relate their personal goals within the wider context. We do not believe that "society" should lightly declare research topics prohibited because they may have troubling implications, or that genetics research has a unique need for such regulation. It will not be easy to predict either what are the insuperable moral problems (if any) or where a given line of enquiry might lead. We do not believe that "hidden agendas" apply more to geneticists than to anyone else. It may be unhelpful to generalise about geneticists as a group—many are leading the public debate on social and ethical issues. The remedy for "hidden agendas" in any area is to catalyse open, educated and rational debate among the public-at-large.

1.4 *Does research into human genetics lead to a deterministic or any other particular view of human behaviour? Will people try to improve the world through genetic interventions? Should they?*

Genetic research does not necessarily lead to a deterministic view of human behaviour. It does increase understanding of the interplay of factors—genetic, environmental, social—that influence behaviour. Conduct of research does not imply that the researcher, company or institution takes a genetic reductionist view. It is the use to which those results are deployed that is critical. Development of genetic medicine does not presuppose a new genetic, reductionist orthodoxy, where environmental and social influences are discounted, since understanding these external forces will be instrumental in achieving a thorough understanding of the pathogenesis of disease.

"Genetic interventions" need to be specified more explicitly. Improving healthcare is a laudable goal. As regards somatic gene therapy, efforts will be made and should be encouraged. As regards germ line therapy, we currently lack a feasible technology and a clear objective.

1.5 *Germ line intervention would affect later generations who cannot give their assent. Are there other objections in principle to it which go beyond our limited knowledge of what those effects might be? Would this be playing God? What does that mean and why would it be wrong?*

In both societal and narrow scientific terms, our knowledge of our own ignorance should make us cautious on potential germ line interventions. While extraordinary scrutiny and firm legislative control would be essential for germ cell modification procedures it may be that most of the issues are perceived, eventually, as practical rather than ethical. The UNESCO International Bioethics Committee is developing a liberal approach (Nature 29 September 1994, p.369; Gene Therapy Newsletter November 1994, p.4–5): germ line therapy may not be a public policy option but banning is premature and unnecessary.

It is important to ensure that human biological diversity is retained. Widespread germ line interventions could pose some long-term risks to the fitness of the species. The concept of "bad genes" is highly misleading. Evolutionary experience with genetic disorders such as sickle-cell anaemia, cystic fibrosis and certain types of obesity indicate that these traits are not unalloyed ills. The sickle-cell trait confers resistance to malaria. A single cystic fibrosis mutation may help the carrier survive cholera. People who are obese in times of abundance are well fitted to times of scarcity.

1.6 *What should the proposed UN declaration and treaty on the protection of the human genome say?*

It may be premature to specify detail prior to current discussions within member states. the UN declaration should also take account of, and integrate, recommendations from other national and international activities on these issues. Some of these pan-national bodies are mentioned in our answer 1.2 but individual countries (e.g., France, Norway) and US States (e.g., California) are also active. The UK must be alert to the possibility that ethics laws passed by individual countries may be unnecessarily coercive, and inhibitory to research.

It seems reasonable for the UN declaration to cover screening and gene therapy issues, as discussed by UNESCO, and it is gratifying to find that the recommendations are likely to be less prescriptive than, for example, the corresponding (provisional) efforts of the Council of Europe. It is essential not to act in a way that

can constrain future research—presently unimagined—or interfere with the current national regulatory efforts, based on a product rather than process-oriented perspective, that work well. In order to achieve consensus, the UN declaration may well have to avoid contentious issues (e.g., abortion; the relative value of voluntary versus mandatory screening; patenting).

We are encouraged by the liberal tone reported in the early UNESCO discussions. We agree with Madame Lenoir, that too much attention has been paid, elsewhere, to the negative aspects of genetics research. As she remarks, a balanced look should consider benefits as well as risks and we support efforts to ensure that the declaration avoids dogma and remains open to scientific progress (Nature 29 September 1994, p. 369).

2. Public awareness and education

2.1 *What is the extent of knowledge of and interest in genetics among different sectors of the public. Should steps be made to improve this and, if so, what form should they take?*

It is our view that the general level of understanding is low. Evidence from surveys of public views on genetics suggests that, in Europe, optimism about genetic technologies is decreasing although public support for the development of new medicines is still relatively robust. In an international survey (Macer, quoted in Gene Therapy Newsletter, November 1994) there was considerable support for genetic screening and for gene therapy for serious diseases, but much less overt support for biological enhancement.

The broad questions—how the public should be provided with information on genetics, who should provide the information (and interpretation) and who should pay for it—are complex. SmithKline Beecham is undertaking part of the job, striving to reach educators, writers and reporters with accurate information on genetics and its applications to human health. We also work, for example with the ABPI, in providing information to schools and, via sponsorship of the Science Museum, in disseminating information to the population-at-large. We recognise the continuing need for novel information vehicles and share the widespread interest in recent UK initiatives as diverse as SET 7 and Consensus Conferences in Biotechnology. These experiments in communication deserve further evaluation.

2.2 *Is there a general anxiety and suspicion about research in genetics? Is it justified or should it be allayed and, if so, how?*

Despite the optimism that might be generated by consideration of the public survey results on genetic technologies in medicine, the ongoing BST and genetically-engineered-tomato debates serve as a demonstration of how fear generated by activists in a biotechnologically-naive population can threaten the introduction and acceptance of new products despite scientific demonstration of safety. Uncertainty creates anxiety; the remedy (answer 2.1) is to inform and educate without patronising or hyperbole. Teaching an elementary understanding of the principles of benefit:risk relationships in the secondary school curriculum might help to improve the operating climate for many high technology industries.

2.3 *Are there unreasonable expectations of the benefits that might come from genetics? If so, should these be tempered?*

It is recognised as a general problem that the short-term implications of technological change, whether in terms of benefits or risks, are likely to be over-estimated whereas the long-term implications are likely to be under-estimated. More specifically, in this area, marketing and promotion activities of over-zealous start-up companies are likely to inflame public fears about the responsibility of pharmaceutical companies as custodians of genomic technology and data. Already, start-up diagnostic companies are marketing genetic tests whose role in medical practice is unproven at best.

We feel that it is unlikely that public reaction and legislation will distinguish the role of SmithKline Beecham or heed our advice on critical issues relating to our ability to conduct and commercialise products resulting from genomics-driven research, unless we establish ourselves as a concerned, active, contributing and responsive force in the assessment of ethical, legal and social issues arising from genomic research and the resulting development of public policy and legislation. We are active contributors to the UK Technology Foresight Programme efforts in exploring consensus (and the basis for dissensus) on S&T issues in human genetics research. We feel that it will be equally important to develop government-academic-industry partnership to explore the bioethical issues and to extend the discussion to the population-at-large (answer 2.2).

2.4 *Is there a danger that genetics will be seen as an excuse for socially unacceptable behaviour? Could it be used to justify reductions in social programmes of health, education and welfare?*

The genetics of social behaviour is not a business focus for SmithKline Beecham. We recognise, however, that the issue of the inheritability of behavioural traits, such as IQ, is a controversial issue. Although this issue

is by no means new it has been recently provoked by the publication of "the Bell Curve" (Murray and Herrnstein). Whatever is ultimately demonstrated concerning the genetic contribution to IQ or other behavioural traits, there is no justification for reductions in social programmes of health, education and welfare. Advances in scientific understanding might enable funding of social programmes to be better targeted. Thus, for example, instead of concluding—if there were a link between race and IQ—that remedial education could not work in certain population subsets (Murray and Herrnstein), we must use education to minimise and reverse biological-based disparities in IQ.

2.5 *What are the right questions on the bearing of genetics on human behaviour, ethics and belief?*

Genetics should be accorded its place as an influence, along with environmental and social influences, in multifactorial diseases and behavioural traits. Many relevant questions have been raised by this select committee enquiry and in the other recent reports in this area, detailed in previous answers.

However, should it be assumed that some questions are "right" and others "wrong"? The distinction between normative ethics (deducing standard ethical principles) and non-normative ethics (what people actually do) is at the heart of this issue. As in all medicine since Hippocrates, questions on genetics and ethics must encompass the issues of voluntariness, informed consent and confidentiality, derived from respect for patient autonomy, equity and privacy. We need to recognise that the relationship between fundamental bioethical principles can be ambivalent, leading to ethical tension (e.g., autonomy versus nonmalfeasance, autonomy versus group welfare).

3. Genetic disease

3.1 *How much of genetic diagnosis is conducted as a routine medical service and how much is associated with research programmes? Is the continuity between the two sufficiently well organised? Are some diseases with a known genetic cause not being diagnosed and, if so, why not?*

Genetic diagnosis is performed as a routine medical service by measuring phenotypic expression in neonatal screening for phenylketonuria and hypothyroidism. This appears to work reasonably well in the UK.

Genetic diagnosis has become established in certain communities or population cohorts with well understood specific risks, e.g., Tay-Sachs disease, ß-thalassaemia, Downs syndrome. Genetic diagnosis at the research programme level is being initiated in pilot studies in the UK (e.g., cystic fibrosis, Huntingdon's disease). An important lesson learnt from these early experiences, at the research programme level, is the need for individual counselling—before, during and after screening.

Because of present cost considerations, new genetic diagnostics still tend to be offered at the research programme level but this will change as reagent costs decline and faster/more economical protocols are designed. The transition from research assay to clinical diagnostic is driven by a conjunction of perceived market need, evolving technology and changing economics.

Many diseases with a known genetic cause are not screened. It has been estimated that there are more than 4,000 diseases that appear to result from the action of a single mutant gene, where external effects play little part. Most of these are not subject to screening programmes, because of their rarity and lack of perceived cost-effectiveness in identification (in the absence of any treatment option).

3.2 *Are there any ethical questions about somatic cell gene therapy which are different from other types of therapy which affect only the patient receiving them?*

This issue has been partly addressed in previous answers. We agree with the conclusions of the Clothier report (and other recent discussions, including those of the UNESCO International Bioethics Committee) that somatic cell gene therapy does not raise new ethical questions.

3.3 *Should information about an individual's genome be regarded as confidential or should it be possible for employers, insurance companies, etc., to require genetic tests or to obtain the results of previous tests on an individual or their relatives? If not, why is genetic testing any different from current medical tests?*

We endorse the recommendations made by the Nuffield Council and the Institute of Medicine (see preamble to question 1).

While it is necessary to recognise that genetic screening may have greater family implications or confer a greater sense of certainty by comparison with other forms of diagnosis, these issues do not detract from the principle that genetic screening should be subject to the same considerations as any other diagnostic approach. Employment issues, for example, are not new.

Train drivers are tested for colour blindness, which is a genetic trait. As regards insurance, a recent editorial in the British Medical Journal urges any moratorium on genetic testing to be extended to all forms of insurance in which underwriting is based on medical risks. This view has inspired a debate on relative morality—would protection from insurance discrimination infringe the rights of others, whose premiums will rise, without consultation? The further examination of these issues in the UK, by the Department of Health, and others, will be valuable.

3.4 *When is population screening for genetic disease appropriate? What factors, such as cost and the availability of counselling and treatment, should be taken into account? How should screening be organised and regulated?*

Population screening is appropriate, if:

- A reliable diagnostic procedure is available.
- The genetic defect is widespread.
- Undetected disease represents a significant risk to the individual.
- Genetic counselling is available to all those tested.
- The results are confidential.
- Effective treatment/patient care is available.

These criteria and other issues relating to the introduction and organisation of screening are discussed in greater detail in the Appendix (Genetic Screening Outside of "Serious" Disease).

3.5 *If screening for a wide range of genetic predispositions becomes routine, how will people be protected from discrimination on the grounds of their genotype? Should they be?*

Careful scrutiny and appropriate legislative control of the risk of discrimination is essential if society is to avoid creating what Dorothy Nelkin has referred to as a new genetic underclass. Discrimination will be best avoided by a commitment to confidentiality and to quality control in testing. As a society, we must also learn to appreciate that the "bad gene" concept is a misconception (answer 1.5), that the gene is not the disease and that a predisposition is not an event.

3.6 Would people be well advised to seek genetic information from sexual partners before the conception of children? Are they likely to? Is this likely to change with future research?

We feel that this question raises issues beyond our ability to offer specific advice. Those individuals most likely to seek genetic information will continue to be those with the most reason to do so—those who come from families with direct experience of inherited disease.

We suggest that governments or other authorities should not be coercive in their requirements for people to seek information (or act in preferred ways)—society must respect individual autonomy and remember the lessons of the eugenic legacy.

4. Economic benefits

4.1–4.4: See Key Questions section.

4.5 *What products, other than medical diagnostics and therapies, might be produced as a result of human genetic research?*

We foresee an integrated healthcare bundle of products and services. Information on health and genetic status could be carried on individual "smart cards" or CD-ROMs for population cohorts and a computer database will advise the medical practitioner on appropriate care and preventative measures. Commitment to genetic profiling carries the responsibility to provide concomitant counselling and information services. Treatment as conventionally understood will, eventually, become an action of last resort, only used when the proactive approach of predict/prevent fails.

The combination of genetics research with economics (health outcomes assessment) will ensure that products are not just safe and effective but also deliver "value". This forces the evolution of new business strategies to embrace the much broader horizon of total pharmaceutical care and disease management.

Fusion of genetics research and bioinformatics will provide other new challenges, possibly for NHS products and services. For example, the delivery of healthcare remotely, whether to the patient's home or to patients abroad, could represent a major opportunity for healthcare services.

The consideration of other potential products, e.g., relating to forensic genetic fingerprinting, is outside our remit and is not covered here.

5. Research

5.1 *Why is it worthwhile to map and sequence the human genome? What are the relative advantages of mapping expressed genes only versus completely sequencing the genome?*

The objectives of the publicly-funded Human Genome Project and the commercial initiatives in genome research being undertaken by numerous companies are largely different. The Human Genome Project in the USA, and similar activities being undertaken with government funding in Europe and Japan, are seeking to construct a detailed map of the total human genome by sequencing the estimated 3 billion pieces of genetic code. This massive research effort is designed to create an exact "road map" that will identify the precise location and sequence of individual genes on each human chromosome. In addition, similar publicly-sponsored efforts are being used to create similar detailed road maps of genes in other organisms, ranging from bacteria to agriculturally important plants and animals.

For further details on the objectives and potential value, the OST Report is recommended. The goal is to sequence the total human genome by the year 2005 but, unless sequencing methods are improved, this aim will not be achieved.

The value of sequencing only the areas of the genome corresponding to the expressed genes has been described in our earlier answers: much commercial genomic research will focus on genes that have yet to be identified by the publicly-sponsored mapping effort.

5.2 *What will it tell us about the human species and the individual that would not otherwise accrue from piecemeal studies?*

The extra information that will be provided by mapping the whole genome has been discussed in the OST Report and we recommend this as a source for detailed information. The only point that will be emphasised here relates to the information arising from the Human Genome Project-sponsored research on the ethical, legal and social issues. Dedication of funding to such research was a bold and creative step for a Big Science project and represents an initiative that will help to catalyse the government-academic-industry partnership in debating all of the issues.

5.3 *To what extent are human characteristics determined by the genome and to what extent does the environment influence the expression of genes?*

It is impossible to generalise on the balance of nature and nurture: each human characteristic has to be considered separately. As discussed previously, we feel that it is important to avoid the hyperbole of deterministic reductionism. We believe that, by better defining the influence of genes in disease, including genes that predispose to disease, we will also reveal a better understanding of the contribution of environmental influences. Progress in understanding has been made recently in major areas like diabetes, hypercholesterolaemia and cancer. For example, by identifying those subsets in breast cancer with a strong genetic component, the environmental influences on pathogenesis in other subsets may be more easily discerned. Prior to this increased precision in subtyping, the aetiology of breast cancer was confusing in its heterogeneity.

5.4 *How much is understood about the organisation of coding information in the genome? Is it conceivable that interventions such as those produced by gene therapy might have unforeseen effects?*

There is rapid progress in understanding the organisation of coding information, e.g., in terms of the influence of promotors and other regulatory elements. Clearly much more remains to be understood and this is a major argument in favour of publicly-funding the Human Genome Project.

Random insertion of genetic material might interrupt regulatory sequences or unintended coding sequences, with disruptive consequences. Hence, the importance of current efforts in vector technology to achieve directed insertion in order to minimise such possibilities, although it is unlikely such concerns could be eliminated with any integrative strategy. As with any other novel therapy, the delineation of the benefit:risk relationship in somatic cell gene therapy proceeds with caution. Our uncertainty on technical factors is a major reason why human germ line gene therapy cannot yet be comtemplated. It is important to remember that gene therapy is only one of the novel types of product and service that will emerge from human genetics research.

5.5 *Is the financial support for research in human genetics adequate when compared with the results which may flow from it?*

Many of our answers describe the potential for health and wealth creation arising from genetics R&D. The UK is a world leader in some areas of basic research but there are causes for concern as outlined in our previous answers. There is one other specific point we would like to make now. The NHS has a research role in collecting family material for gene mapping, pedigree analysis and other genetics research. This role may be adversely affected by the funding implication of the internal market reforms. If this expertise is allowed to decline, the UK will be at a competitive disadvantage relative to the US where the SME sector has developed to engage in these types of pedigree research.

We also want to reiterate one general point. Public investment in basic genetics research cannot be considered in isolation from the private investment made by companies in their attempts to develop innovative products and services. Public funding will have little value if companies cannot appropriate the technological advances because they do not see clear strategic goals. The climate for investment deteriorates if uncertainty is allowed to prevail. That is why we welcome the present enquiry in identifying and clarifying these most important ethical, social and regulatory issues.

6. Evolution

We do not feel sufficiently qualified to offer specific views on these topics.

Memorandum from The Wellcome Trust (HGC65) (12 December 1994)

In recognition of the importance of genetics research and the medical and social implications thereof, the Wellcome Trust has established a Genetics Interest Group, chaired by Sir David Weatherall, to advise the Governors on any matters germane to research in and involving genetics. In addition, the Wellcome Centre for Medical Science has identified genetics as a priority area for its communication and education programme.

Human genome mapping project

The Wellcome Trust is represented on the Office of Science and Technology's Advisory Committee on Human Genome Research and has contributed to the report commissioned by the OST entitled "The Human Genome Mapping Project—Priorities and Opportunities in Genome Research". Many of the questions raised by this inquiry in relation to the Human Mapping Genome Project have already been addressed in this report, which was published in April 1994.

The Wellcome Trust has committed substantial funding to the establishment of two key centres in the UK involved in genome research. Together with the MRC, the Wellcome Trust provides support for the Sanger Centre at Hinxton Hall, near Cambridge, which is involved in sequencing and mapping the human genome, as well as sequencing the worm *Caenorhabditis elegans* and yeast. The Wellcome Trust's current commitment to the funding of the Sanger Centre is approximately £44 million over five years (excluding capital building costs). The European Bioinformatics Institute (EBI), an outstation of the European Molecular Biology Laboratory (EMBL) will also be located at Hinxton Hall following the successful bid from the UK Government made in partnership with the Wellcome Trust and the MRC. In Oxford, the Wellcome Trust has provided funds to establish the Wellcome Trust Centre for Human Genetics to study genes involved in complex diseases such as hypertension and diabetes; the Trust has agreed to provide approximately £14 million over five years (excluding capital building costs) to establish this centre.

General, ethical and regulatory

Research in the field of human genetics moves very rapidly and, consequently, the way in which particular ethical and regulatory issues are perceived also changes rapidly. In order to address these issues adequately, it is necessary to take both our current knowledge and the potential of future research into account. It is, therefore, recommended that the Government should seek to establish regulatory framework to monitor research in this area and address specific ethical issues as they arise, consulting with the public, as appropriate. This would hopefully provide the necessary consistency and stability to ensure that public concerns are adequately addressed. The Trust, together with the MRC, contributes to the financial support of the Nuffield Council of Bioethics which published a report on the ethical issues of genetic screening in December 1993. The Trust's Genetics Interest Group has endorsed the recommendations of that report which include the recommendation that a

central co-ordinating body should be established to review genetic screening programmes and monitor their implementation and outcome; the remit of such a body might reasonably be expected to include other aspects of genetics research rather than just screening programmes.

Public awareness and education

The 1993 Gallup Poll on genetics revealed that only 5 per cent of those interviewed considered themselves to be very knowledgeable about genetics although 42 per cent described themselves as reasonably knowledgeable.

The 1993 Eurobarometer Survey of public attitudes to biotechnology and genetic engineering revealed that 48 per cent of interviewees believe that "genetic engineering will improve our way of life in the next 20 years", this optimism was found to be a positive function of the objective knowledge respondents had of the subject. However, more than 75 per cent of respondents considered that "there should be clear ethical rules" indicating when research "may not in any way be undertaken". Less than one respondent in five believed that Public Authorities provide a reliable source of information regarding genetic engineering; this highlights the need for any regulatory body to establish public confidence as a matter of priority.

Against this background, the Wellcome Trust endorses the recommendations of the Nuffield Council on Bioethics which call for an improvement in the public understanding of human genetics in order to safeguard against eugenic abuse of genetic screening and to prevent stigmatisation of those carrying or suffering from genetic disorders. In order to ensure adequately informed consent of individuals participating in genetic screening programmes, research is required to determine the most effective ways to communicate genetic information and counsel individuals appropriately.

The Wellcome Trust, through the Wellcome Centre for Medical Science, is taking an active role in promoting the public understanding of genetics, with projects aimed at further elucidating the knowledge and attitudes of the public and a programme of prominent exhibitions around the country.

Genetic disease

The psychological and social impact of screening for genetic disease has not yet been evaluated and is likely to vary enormously according to the nature of the disease, the predictive power of the test, the therapeutic possibilities and many other factors. In the light of this, it would not be appropriate to make generalised statements about when and how population screening might be appropriate. It is, however, essential that an effective regulatory mechanism is put in place to ensure that individual screening programmes are monitored and evaluated on a consistent basis and that adequate resources are provided to ensure that patients are adequately informed and counselled throughout the screening process.

Economic benefits

The Wellcome Trust has committed substantial funds, *via* the Sanger Centre, to the support of human genome research in the public domain. It is currently questionable whether the commercialisation and privatisation of human genetic information is likely to facilitate health care benefits or impede transfer into the health service. The Trust is strongly opposed to the patenting of DNA sequences of unknown utility and also to the patenting of natural, normal human DNA sequence *per se;* whilst a DNA sequence may provide supporting evidence for an invention, the ability to patent natural human DNA sequences raises many ethical and moral issues as well as creating potential obstructions to the development of health care benefits. Consequently, the Sanger Centre, which is supported by the Trust to carry out human genome sequencing, does not file patents on human DNA sequences, as a matter of policy.

Memorandum from the Down's Syndrome Association (HGC68) (15 December 1994)

Thank you for inviting comments for the above inquiry. The Down's Syndrome Association is most concerned about the use of antenatal screening tests for Down's syndrome. Of the questions circulated with the invitation to comment, 3.1 and 3.4 closely reflect our concerns.

Down's syndrome is a genetic condition that is rarely inherited. Recently antenatal blood serum and ultrasound screening have been developed, to use in conjunction with diagnostic tests, principally amniocentesis, which has

been available for some time. I have enclosed a copy of our publication, "Pre-natal Testing for Down's Syndrome" for your information.

The Down's Syndrome Association exists to support people with Down's syndrome and their carers. We do not believe that carrying a child with Down's syndrome is a reason to terminate a pregnancy, but we accept the right of the individual to make an informed choice on this matter. We receive an average two to three calls a day from pregnant women and their partners requesting information and counselling about tests. Hence we gather a lot of information on the experiences of couples in different parts of the country.

Both types of screening test are becoming increasingly available. In some areas they are routine and free, in other areas information is given on how to purchase the tests privately. In some areas no mention is made of the tests to pregnant women and only those well informed couples are aware of the private services available.

We are concerned about this inequity in the provision of the service.

We are aware of two centres offering the blood test privately to anyone anywhere in the country who is prepared to pay. These centres are at the fore front of the research in their field in which their is a great deal of activity aimed at producing increasingly sensitive tests.

We are aware of one centre carrying out research into ultrasound screening. It appears that this centre will offer a service to people from any part of the country.

We are concerned about the appropriateness of the dual role of the centres to provide a service to a potentially very vulnerable sector of society and to furthering their research aims. We also are concerned about the commercialisation of these tests.

The quality of information and support services available to those expressing an interest in the tests is very varied. Those areas now offering the test routinely do not always seem to be meeting their patients needs for information on the tests or on Down's syndrome. Nor do the training and support needs of the staff appear to be being addressed adequately. Where the test is purchased privately a telephone counselling service is offered. This seems inadequate given the nature of the decisions being made. Local health professionals such as GPs are honest about feeling ill-equipped to offer the counselling required.

We therefore feel that the true cost of running a screening service must take into account adequate funding for patient counselling and staff training.

We are conscious that a crude cost-benefit analysis of the number of babies with Down's syndrome terminated as a result of widespread screening and the implied long term savings this provides may be a false assumption.

Our main concerns are therefore: the inequity of provision, the close association between research, service provision and private enterprise, the inadequacy of support, information and training, and cost of service versus numbers of babies born.

We recommend that a regulatory body is established to ensure that the introduction and provision of testing is monitored so that high and consistent standards of service provisions are attained.

Memorandum from The Progress Educational Trust (HGC71) (16 December 1994)

Introduction to progress

The Progress Educational Trust is a registered charity formed in 1992 following the establishment of the Human Fertilization and Embryology Authority. The main aim of the Trust is to educate the general public, parliamentarians and professionals on all aspects of research using the human embryo, in order to encourage informed and reasoned discussion on the issue. The Trust is a source of information for infertile couples, those at risk of genetic disease, students, parliamentarians and the media.

There are a number of questions in the Science and Technology Committees Press Notice on Human Genetics that fall within the educational role of the Trust. Our response focuses on topics where there is overlap between Genetics and Embryo Research.

PUBLIC PERCEPTIONS: HUMAN GENETICS AND EMBRYO RESEARCH.

(see questions 2.1, 2.2)

Since the main role of the trust is in disseminating information about embryo research we wish to clarify a common misconception held by the general public that research using the human embryo and genetic research are inextricably linked. This is not the case. One of the few examples where genetics research has been performed on the human embryo is in the development of preimplantation diagnosis. Current application of preimplantation diagnosis as a means of genetic screening is not categorised as embryo research since the technique has been proven. Any notion that embryo research and genetics research are one and the same should be strongly discouraged.

CORRECTING THE GENES: SOMATIC AND GERM LINE THERAPY.

(see question 1.5)

One of the most controversial issues confronting scientists policy-makers and the public is the use of gene-therapy for the treatment of genetic disorders. Somatic cell therapy, which does not involve research on the human embryo, is aimed at correcting the abnormal gene in the cells that require the gene to function normally. In this case the corrected gene is not passed on to subsequent generations, but the abnormal gene is and will therefore contribute to genetic abnormalities in subsequent generations. Correcting the gene in the germ cells so that future generations inherit the normal gene is known as germ-line therapy. This may involve research on the human embryo but such research is currently outlawed. Thus, somatic cell therapy is considered acceptable and is in clinical trials while germ-line therapy is banned. This is a sensible strategy to adopt since the success of somatic cell therapy is still under evaluation. If somatic cell therapy is widely successful the question will be raised as to the possibility of germ line therapy so that defective genes can be eliminated from families forever. This is a question that will require careful thought and reasoned discussion, in the social, ethical and scientific contexts.

Genes, germ cells and epi-genetic modifications.

(see question 5.3)

The Human Genome Project aims to sequence all of the genetic information in the human genome. The implications and potential use of this information is vast but is often mistakenly portrayed as being the key to unlocking the "secrets of life". Unfortunately knowing the code does not provide all the answers. The complex questions arise when we begin to ask how genes are regulated and how they interact. There are several examples of how genetic disease is susceptible to environmental, or epi-genetic, modifications. The Human Genome Project does not involve research on the human embryo, however, such research is important in understanding aspects of epi-genetic regulation of gene function.

Genomic imprinting is a means of genetic regulation whereby the expression of a gene is dependent solely upon the parent from which it was inherited. Normal expression of imprinted genes is essential for embryonic development and a number of imprinted genes have been implicated in human genetic disorders such as Prader-Willi syndrome, and Angelman syndrome. Imprinting occurs during the development of the male and female germ cells and is modified during early embryonic development. Research on germ cells and early mammalian embryos will help to determine precisely how genes are imprinted and when the imprinting occurs. This information is essential for a complete understanding of the contribution of imprinted genes to human development and genetic disorders.

The implications of epi-genetic regulation of genes to genetic screening is that there will be many genetic disorders not amenable to current approaches to genetic screening. This problem is also apparent in poly-genic disorders where abnormalities are a result of several different interacting genes.

Memorandum from Glaxo Holdings Plc (HGC72) (15 December 1994)

The Committee's inquiry into human genetics covers an extremely wide range of areas in which the recent advances in our understanding of human genetics will have an impact. Of particular concern will be the new knowledge being provided, almost daily, as a result of the international Human Genome Programme. Information about human genes, and more particularly its potential use, does have far-reaching social, ethical and legal implications which must be addressed. However, the expansion of genetic knowledge also has considerable potential to bring medical benefits to the community. These range from the provision of powerful new diagnostic tools to allow early detection of disease or disease susceptibility, to more certainty for those

providing genetic counselling services and also to the discovery and development of new medicines. It is also important to understand the impact which the availability of genetics-based information will have in other areas of community life such as life assurance and employment and there will no doubt be other ways, as yet not known, in which the knowledge of the human genome may come to be used by society. However, great care must be taken to ensure that the real benefits for mankind that lie in the advances in biology and medicine, and particularly those which are to be gained from research in the area of genetics, are not allowed to be stifled by concerns about the possible detrimental, or wrong, uses to which results of this research may be put. There is a need to develop a considered and balanced view of developments in this exciting field of science and technology and for such sensible regulatory measures to be taken as society will require, without prejudicing useful scientific and medical advances in the UK. We therefore welcome the Committee's present inquiry which we believe to be timely.

In this memorandum we offer the Committee the views of this Company about the value of human genome research but it will, of necessity, be limited to a consideration of the use of new genetic information in the prevention and treatment of human disease.

Human Genome Research and the discovery of new medicines

Glaxo is a science-based pharmaceutical company and we believe that our future success will depend on our ability to discover and develop innovative medicines that will meet the needs of the global community and provide real therapeutic benefit. Most of the medicines that are currently available for the treatment of common chronic human diseases are able to provide only palliative treatment for patients. For example, the nonsteroidal anti-inflammatory drugs are able to relieve symptoms in the patient with rheumatoid arthritis but they do not arrest the disease process and prevent disability; anti-hypertensive medicines reduce blood pressure without affecting the disease processes causing the hypertension. In other clinical conditions affecting significant numbers of people there are no safe and effective curative treatments. Diseases of the central nervous system such as Parkinson's disease, the senile dementias and schizophrenia, or the musculoskeletal system such as osteoarthritis, osteoporosis, muscular dystrophies or metabolic diseases such as non-insulin dependent diabetes are but a few examples of the challenges that face both clinical medicine and the pharmaceutical industry.

If we are to meet these challenges then the search for new medicines must begin with an understanding of the cellular and molecular process underlying these conditions. Only when we have achieved this goal will it be possible to identify novel molecular targets against which new drug molecules can be directed to ensure significant amelioration and even cure of such diseases. The major advances that have been made in the fields of molecular and cellular biology and biotechnology over the past 10–15 years have resulted in an explosion in our knowledge of biological processes. We are now moving towards being able to apply this new knowledge to defining targets for therapeutic intervention.

The information that is now emerging, and will continue to emerge, from the Human Genome Programme is an essential part of the process of understanding human disease, and it will contribute significantly to future methods of treatment. This may be expected to be either directly, through gene therapy, or indirectly, through the development of medicines to control the activation of a gene or the expression of its product in the cell or, even more indirectly through the discovery of medicines which can interact beneficially with the cellular products of disease-associated genes. Similarly, the studies of the genomes of other organisms, particularly disease-causing bacteria, viruses and parasites, which are going on in parallel, may also be expected to lead to the definition of molecular targets against which effective medicines may be discovered or designed.

Glaxo's involvement in Human Genome Research

Glaxo, through its "Human Genome" initiative is making a major investment in human genetics and genome research. In our UK laboratories we have developed facilities for human genome studies and now employ 27 scientists and technologists directly involved in the positional cloning and sequencing of human genes and a further 6 specialists who are involved in providing the vital bioinformatics facility that genome research requires. Our total investment in this area of science now amounts to about £6 million per year. The nature of the study of the human genome of necessity requires access to well-studied and defined families showing inheritance of disease-linked genes. Thus we are developing collaborations with clinical genetics groups in academia who have the necessary families and the skills for gene identification and mapping. This is a field in which, we believe, close partnership between university clinical scientists and industrial research scientists is essential for success. We have, therefore, established a major collaboration with scientists at Duke University, North Carolina, in the field of Senile Dementia of the Alzheimer's type (SDAT) in which we are investing about $1.3 million dollars per year for five years. We are also planning to commit a significant sum of money to support a human genetics collaboration with a unit in a UK university. We will develop further academic partnerships in the genome field as appropriate opportunities arise. In addition we have strategic alliances with two biotechnology-based genome companies in the USA in the fields of diabetes (Sequana Therapeutics) and migraine (Spectra Biomedicals)

which together will cost about $3.5 million per year over the next 3 years. We are also investing $1.0 million a year in a collaborative study of gene therapy in cystic fibrosis with Megabios, another US company.

Mapping the Human Genome

A question asked by the Committee is: is it possible to obtain useful information without mapping the whole of the human genome? The answer to this must be yes. Thus the gene for the transmembrane conductance regulator (a chloride channel in the cell membrane) which is defective in Cystic Fibrosis, and also the gene for the enzyme adenosine deaminase, which is deficient in a form of immunodeficiency disease, have both been identified, isolated and are in use in clinical trials of gene therapy of these conditions. These are however examples of diseases which have a single gene defect underlying them. It may be expected that other single gene diseases will also prove susceptible to this "piecemeal" approach. But this approach to understanding the genetic basis of disease will be limiting. Many of the common diseases are not due to single gene defects and probably have several different genes underlying them, with the disease being the result of the interaction of their cellular products. The genes involved in such multigenic diseases are most likely not to be located near to each other or even on the same chromosome. Their involvement in disease processes, and the identification of the key interactions, will only be possible through careful mapping of genes of affected families. Furthermore the control of the "switching on" of a gene and expression of its product in cells will be under close control of neighbouring sequences of DNA. It is important that these sequences, or the sequences of possible "regulatory" genes are also identified. Such information could lead to the discovery of drug molecules capable of very specific control of gene function by acting as "gene switches" for disease associated genes. The mapping of the whole genome will considerably assist our understanding of complex interactions which will not be revealed easily by the piecemeal approach.

It is also very probable that diseases which we regard today as being relatively homogeneous entities, are in fact merely the similar manifestations of a number of different abnormal gene-determined mechanisms. This would be important to recognise because the different genetic "subtypes" of a disease may require very different types of drugs to be used. For example, it is now becoming clear that there is more than one type of SDAT with regard to the genes involved. To be able to diagnose the genetic type of SDAT would allow the tailoring of a drug approach to be used for a particular patient. Such anti-SDAT medicines do not yet exist, but information from the genetic studies could indicate the molecular targets for drug design. Then, once such a drug candidate is available, the ability to identify those SDAT patients with the particular genetic make-up would increase the precision and sensitivity of efficacy-proving clinical trials. At present there is usually no way of selecting patients with major multigenetic diseases in the clinical trail process.

We would suggest therefore that, although the mapping and sequencing of the entire human genome is a research intensive and costly project, the outcome will be of immense value in understanding, preventing and treating human diseases. It could open the way to the discovery of new drugs which would be curative for common, and economically important, diseases. It is also a programme in which there is a sense of urgency with considerable competition between laboratories to discover disease-related genes and to be first to publish or, in some cases, to patent. It must also be stressed that genomic research is an international activity and there are now a number of major research organisations established in the USA and Europe to search for genes. If the UK is to be competitive in this field it is important that encouragement is given to the UK centres of excellence in genetics and the human genome initiatives which are being supported by the Research Councils and medical charities.

A strong bioinformatics resource is needed to handle and analyse the great amount of data which is generated by analysis of the elements of the human genome. The relocation of the European Bioinformatics Centre to Cambridge is of major importance and also testifies to the standing of the UK science base in this area. It is however important that UK genome researchers in both academia and industry have access via the IT networks, such as Internet, to the international genomic databases relating to both the human and other species. It is also essential that genome data generated by UK groups contributes to the international pool to ensure the completion of the Human Genome mapping project as soon as possible.

Science and Technology ancillary to the exploitation of Human Genome data

In order that the full value of the human genome data is obtained for the UK we must have other scientific and technological capabilities available. For example, we should be able to introduce human disease related genes and other genes into animal species by the use of transgenic techniques. This is needed for a number of reasons ranging from the production of human proteins on a large scale, in for instance animal milk, to the establishment of more precise and relevant laboratory models of human diseases. The availability of such models would allow laboratory validation of the gene and its product as a therapeutic target, and also an early, and more reliable, assessment to be made of efficacy of new drug candidates or treatment regimes. The production of a transgenic mouse model of Cystic Fibrosis, for example, made assessment of gene delivery systems in the laboratory possible before embarking on clinical studies. In addition to the scientific and technological aspects

of transgenic research, which present challenges in themselves, we must ensure that there are no increased regulatory hurdles placed in the way of such research. It would be counter-productive to impose additional requirements on the development and use of transgenic animals in research other than those which already apply to the use of animals in experiments.

Another area of expertise that will be needed for successful development of gene therapy will be in the field of gene delivery vehicles to bring about the safe, and possibly targeted, incorporation of the gene sequence into the affected cells of the patient. Viruses provide one source of such delivery vehicles. Thus there is a need to ensue that molecular virology is developed in the UK and is well-supported. There will also be a requirement for facilities to produce the genetic material for clinical use which must be of high quality and in sufficient quantities and in the optimum formulation. This will require investment by companies, some of which will be small biotechnology companies, in new plant.

Regulation of Human Genetic Research

We must accept that there will be a need for regulation in the field of human genetics. Aspects likely to be covered will range from issues of confidentiality of, and access to, information about an individual's genome to the control of genetic procedures in the research laboratory and the clinic. There is no reason why the issue of confidentiality of data regarding individuals should present any problems which are not already addressed in current practices surrounding the use of medical information and access to medical records.

Information about chromosomal abnormalities in individuals has been included in medical records for at least the last twenty five years without problems. There is no reason why genome data acquired about patients in clinical practice should be treated in any different way. The most serious problem regarding availability of data about disease-associated genes lies in the *uberrima fides* disclosure required by life assurance companies and healthcare providers. This is an issue which has to be addressed with these organisations. Again, however, this is not a unique issue, having already been encountered in the context of HIV. It is important that they understand the context and true significance of genetic data relating to disease susceptibility and are able to put it into perspective.

We would urge that any regulation which is deemed to be necessary in the area of human genetics should be based upon firm scientific and technological foundations. Over-prescriptive measures should not be put into effect which will have the effect of impeding progress that can be made, particularly in the field of medicine and therapeutics, by use of knowledge of the human genome and the molecular mechanisms by which genes are controlled. The House of Lords recently drew attention to the effects that the over-cautious regulation of biotechnology has had. These regulations have had an inhibitory effect on the development of biotechnology in the UK and it is suggested that they may have had some part in our tardiness in developing a significant biotechnology industry. It is important that in the regulatory field, as in some other areas, there must be a "level playing field" if UK science and technology is to develop successfully in the international arena. Our concerns about over-prescriptive regulation applies also to the European Union and we hope that the UK Government will use its best endeavours to ensure a regulatory climate which is supportive of biotechnology, and particularly of genomic research and development.

Patenting human genes

The patenting of human genetic material is at present the subject of considerable debate in the industry and in academia. In order to protect its commercial interests Glaxo is prepared to patent whatever is needed to retain an exclusive position in any medicines we discover and develop in the future. We are prepared to patent human genetic material provided that it meets the well-established criteria for patentability i.e., that there is an invention and that it has commercial utility. There is no reason why human genetic material, or any other product of biotechnology, should not be considered to be patentable provided it fulfils the criteria for patenting mentioned above. In many, if not most cases however the fruits of genetic research can be placed in the public domain so that the information is available for validation by other researchers and may also be used to amplify our knowledge of the human genome and particularly of disease-related genes. We would be prepared to make patented genes freely available to other research groups. We would prefer that the industry, recognising the value of the information to be derived from genetic research, should be prepared to provide resources, within appropriate partnership arrangements, for global research in this field, as has been suggested recently by Merck.

Economic benefits from genetic research

Gene therapy is likely to offer a new method of treating some diseases which have a clear-cut genetic basis and where a single gene is involved. Generally, however, these diseases do no affect large numbers of patients. In the event that major cancers can clearly be shown to be linked with specific genes, e.g., the recently defined "breast cancer" gene, then it is possible that gene therapy may offer a therapeutic approach for larger numbers

of patients. However, a limiting factor for gene therapy is the ability to deliver the gene to the affected tissue in such a way that it can be incorporated into the DNA of the target cells. This may prove difficult to achieve. In the case of ADA deficiency disease, mentioned above, the gene can be introduced relatively easily into the defective blood lymphocytes by a short period of tissue culture and then returning them to the bloodstream of the patient. However, in the case of Cystic Fibrosis such a tissue culture approach is not possible because the target cells are in the lung. It is possible however to deliver the gene to the lung by means of aerosol inhalers, a common form of drug delivery to the lung, and hope that a sufficient number of lung cells will incorporate the gene to produce relief. However, the Cystic Fibrosis patient also has the same defect in the cells of the pancreas which results in digestive disorder. Delivery of the gene to these cells is likely to be significantly more complex. For diseases such as Huntington's Chorea the gene has been identified, but its function has not yet been clearly established. It is likely however that for use as gene therapy in this disease it would need to be delivered to cells in the central nervous system which is likely to prove to be a very difficult challenge. The economic benefit to be obtained by the use of gene therapy *per se* is thus not likely to be great, given the relatively small numbers of affected people who could be treated, and the potential cost of special delivery techniques that may be needed. Furthermore, a single treatment will be effective for the life of the cell incorporating the gene and so it is most probable that the treatment will need to be repeated at regular intervals. The only way in which gene therapy could be effective as a curative treatment would be if the gene could be introduced into the embryo at the earliest stages (before the defect can be diagnosed by present techniques) or by introduction into defective germ cells.

Genes will also find clinical use in areas other than through gene therapy as described above. They may be introduced into the body in a way that permits them to enter cells which can then act as "factories" to produce the product of that gene where the patient is unable to synthesise the product naturally. For example, in the case of diabetes the use of the insulin gene in this way could allow the production of insulin by the insulin deficient patient.

Of very much more significance would be the new medicines that could be discovered through the light that genome research will throw on disease processes. Such medicines should offer the benefit of curative therapy or, at least, significant amelioration of symptoms. They could also be aimed at those chronic diseases with a high level of morbidity and which affect significant numbers of people, causing disablement and dependency on the community. For example there will be obvious economic benefit to be derived from reducing the level of morbidity and prolonging productivity and independence in patients with diseases such as rheumatoid arthritis, osteoporosis, schizophrenia and the senile dementias.

There is no reason why small molecular weight medicines derived from genome research should cost any more, or less, to develop than other medicines currently in development. They will be required to meet the same stringent standards of proof of efficacy, safety and therapeutic value that medicines in our development pipe-lines today have to meet. The cost of products arising directly from biotechnology, *viz* genes or proteins, is likely to be higher than most conventional medicines because of the methods of production employed. Over time however as production technology develops less expensive processes may be available.

Knowledge of disease-related genes will also provide new means of screening populations and early diagnosis. This could allow early treatment to be given and disease processes arrested or slowed down. Gene-related diagnosis may also provide the possibility of much greater precision in the way a patient is treated in those diseases where there are genetically distinct variants.

Economic benefit is also to be derived for the UK by ensuring that the country continues to have a strong pharmaceutical industry. As the pharmaceutical market-place is essentially a global one and the UK represents less than 10 per cent of it, the industry is a major exporter and makes a substantial contribution to the UK's balance of trade. Glaxo's own contribution to the balance of trade in the last year was in excess of £1 billion. We believe that we can only maintain this position by using the advances being made in the biomedical sciences effectively. The unravelling of the human genome is now a significant source of new knowledge and hence we, and other UK pharmaceutical companies, are making significant investments in this area of research. However we do require a climate which encourages industry/academia collaboration and where technology transfer is encouraged and enabled. The UK is handicapped however in this, and other areas of biotechnology, in having a poorly developed Biotech SME sector compared with the USA to which we must turn for most of our strategic alliances in genome and biotechnology.

Ethical Issues and Genome Research

The increased understanding of the human genome undoubtedly raises questions of how such information will be used in society. There will have to be a broadly based debate surrounding such questions within society and this industry must play its role in this process. In this memorandum we can only address those issues which most closely affect the treatment of human disease.

As far as somatic cell gene therapy is concerned, we cannot see that any significant moral problems will arise. As mentioned above, such treatment may afford relief for some patients with diseases due to single aberrant

genes. However on the basis of present knowledge the effect of the treatment is unlikely to last for longer than the life of the cells which receive the genes during treatment. There should be no longer-term effects on the genetic make-up of the individual provided that local or tissue specific gene delivery methods are used. At present only local gene delivery systems are a possibility and so wider genetics effects are not a significant consideration. However, should systematic gene delivery become possible then there will be the possibility of gene incorporation into germ cells; steps will then need to be taken to assess this risk during the development process for particular gene therapies.

Germline intervention would provide the advantage that a genetic defect could be corrected throughout the body and so obviate the need for repeated gene treatments. However, we would advise caution in this area of genetic research. Firstly there are the obvious eugenic dangers of misuse of the technology to manipulate populations genetically. Secondly, we do not yet understand the interactions between genes and so there may be a risk of unanticipated biological effects. Therefore, we believe that the present international moratorium on genetic manipulation of human germ cells should be maintained for the present but should be kept under constant review. If such research does come to be desirable, or allowed, it will be an area in which there should be careful regulation.

As far as lack of assent of future generations are concerned, we do not believe that genetic research raises any special problems. It is little different from many other areas of biological and medical science which have attendant risks for the unborn generations, such as for example the use of *in vitro* fertilisation or abortion. We must accept however that the use of genetic information does raise particular sensitivities in society and that the scientific community must recognise this.

The use of genetic information to screen for particular diseases, or disease susceptibilities does raise issues, some of which have been briefly touched on above, which must be addressed by the wider community. One matter that should also be considered is the fact that apart from the single gene diseases, which can be treated by gene therapy once the gene is identified, new medicines arising out of genome research are not likely to be available for many years after the gene is available for diagnostic use. This gives rise to the problem of screening and diagnosis before there is any hope of treatment for the condition. For example, under these circumstances what would be the value of screening for genes predisposing to heart disease, or to SDAT, in later life?

The Public and Genetic Research

It must be recognised that there is little understanding on the part of the general public of what genetic research and the Human Genome Programme is about. In the absence of understanding it is expected that there will be increasing concern, and even fear, about what the scientific community is doing. We have already seen this in the hostility to the use of genetically engineered food products, such as the flavour-saver tomato. There will be inevitable suspicions on the part of the man or woman in the street and there is a hidden agenda. We are not however aware of any. The only way that fear and suspicion will be allayed is by the scientific community being prepared to explain to the public what they are doing in as simple and clear a language as is possible. The scientific community—whether in industry, academia or government departments—must also accept the responsibility for ensuring that non-scientists taking decisions affecting the use of science and technology outcomes are able to make informed decisions. It must however take care to avoid the hyperbole that seems at present to be the inevitable accompaniment of the announcement of any scientific advance, such as we experience when a new gene or gene product is discovered. Such overstatements raises expectations and, when the promised benefit is not delivered, it raises scepticism in the minds of many about the value of science, and so is harmful to both science and the community at large.

Conclusion

We believe that the mapping of the human genome, and the information that is being derived from it, offers an important opportunity to understand human diseases. From this understanding we are confident that new therapeutic targets will be identified which will lead to the discovery and development of important new medicines to cure or alleviate common chronic diseases. It is therefore essential that a climate is created which will allow the optimum use of this new information. This will involve collaboration between the pharmaceutical and diagnostic industries with leading research groups in UK universities and research institutions and also with emerging biotechnology companies. In order to ensure that progress towards our goals is made as rapidly as possible regulatory restrictions should be kept to a minimum and should be based on informed opinion. We accept that this is an area in which significant ethical and moral issues will emerge. Again, we believe that these must be addressed but in an informed and balanced way to achieve the greatest degree of benefit of society. The scientific community must be encouraged to engage in free and honest public discussion regarding their activities in this sensitive field to allay fear and suspicion and to create a well-informed and interested population.

Memorandum from British Biotech Plc (HGC73) (15 December 1994)

INTRODUCTION

What is the involvement of your company in genetic research? Have you any products currently in development based on such research? Approximately what proportion of products under development does this represent? Do you expect to develop such products in the future? If so, will you do so in house, through collaboration with academics or through acquiring IPR? Do you expect to carry out such activities in Europe, North America or elsewhere?

British Biotech plc is a leading UK research and development company in pharmaceuticals. Founded in 1986, British Biotech was the first biotechnology company to have its shares listed on the London Stock Exchange. British Biotech's shares are also quoted on the NASDAQ as American Depositary Receipts, each ADR representing two ordinary London shares. The Company is located in Oxford, UK, and has recently established a subsidiary, British Biotech Inc, in Annapolis, Maryland.

The Company employs just over 300 staff, has a market capitalization of approximately £270 million and following a fully underwritten Rights Issue completed in May, 1994, has cash reserves of approximately £58 million. Since its inception, British Biotech has combined the techniques of medical chemistry and pharmacology with those of genetic engineering. The Company has used these techniques to pursue product-focused research in cancer, inflammatory and vascular diseases, and virology.

British Biotech currently has five new pharmaceutical products in human clinical trials, two of which are in Phase III clinical trials, one of which is currently progressing through Phase II testing, and all of which are aimed at substantial pharmaceutical markets:

- Batimastat, an anti-invasive cancer drug is currently in Phase III trials for intra-abdominal malignancies.
- BB-2516, a second generation oral anti-invasive cancer drug is in Phase I trials.
- BB-10010, a Stem Cell Protector for use as an adjunct to cancer chemotherapy.
- Lexipafant oral, a potent PAF antagonist being developed as an anti-asthma drug in collaboration with Glaxo.
- Lexipafant iv, an injectable version of the same entity is in Phase III clinical trials in acute pancreatitis.
- p24-VLP adjuvanted, a post-infection AIDS vaccine, currently undergoing multinational Phase II studies in asymptomatic HIV positive patients and in patients with clinical AIDS.

British Biotech also has additional products in preclinical development including: a dual acting, matrix metalloproteinase and tumour necrosis factor inhibitor, which is being developed as a disease-modifying oral anti-arthritic drug; and TAPgen, an innovative new anti-thrombotic agent with unique properties.

British Biotech routinely uses genetic engineering in its research and development. In this context, genetic research is specifically taken to mean products developed for gene therapy. However, British Biotech has extensive experience in genetic engineering in both its research and development programmes. For example, in research, genetic engineering is used to optimise and improve natural biological proteins, or to develop entirely novel molecules with new therapeutic properties, such as TAPgen, which displays both anti-thrombin (i.e., prevents blood clots forming) and anti-thrombolytic (dissolves blood clots) activity. In development British Biotech has two genetically engineered products, BB-10010 and p24-VLP, both of which are produced in yeast cells. BB-10010 or Stem Cell Protector is an innovative genetically engineered drug that has been designed to mimic the natural human stem cell inhibitor protein. Stem cell Protector acts to prevent the division of stem cells and can therefore protect them from the effects of cytotoxic agents (as used in cancer chemotherapy), which affect rapidly dividing cells. The second product, p24-VLP, is made from a genetically engineered VLP or Virus-Like Particle composed of an inert particle-forming yeast protein to which the HIV protein, p24, is fused in such a way that the particles display the viral p24 on their surfaces. When administered by injection these p24-VLPs stimulate antibody and T-helper cell responses.

Before responding to the specific questions it is worth mentioning some of the potential benefits of gene therapy. Gene therapy could be used in a variety of disorders including thalassaemia, ADA (adenosine deaminase) deficiency, Gaucher's disease, haemophilia A, haemophilia B, cystic fibrosis, muscular dystrophy, hypercholesterolaemia, phenylketonuria, lysosomal storage disease, emphysema and various other metabolic disorders. Various cancers, diabetes and many other diseases, including recurrent viral diseases could also become the target of gene therapy at some stage in the future. A number of companies are in development with gene therapy products in the United States with targets such as malignant melanoma (Vical) and ADA Deficiency (Genetic Therapy).

1. GENERAL ETHICAL AND REGULATORY

1.1 *What do we need to know about the way genes work in order to make decisions about the use or regulation of genetic information? Are we likely to obtain that information?*

We take this question to refer to access to an appreciation of information on the human genome rather than the regulation of gene expression *in vivo*, although in respect of the latter, it should be noted that the operation and regulation of genes is complex, with many different types of regulatory and expression systems found in nature. However, we probably know enough about the important structural elements of genes, including regulatory sequences to enable us to make decisions about the use or regulation of genetic information.

On the question of access and utilisation of such information, DNA sequences from the human genome are being generated in several countries and many laboratories, some of which are commercial. Such is the pace of progress that it is almost certainly too late to devise and implement regulation for access to the public database particularly on an international basis. Commercial interests are also involved. SmithKline Beecham (SB) have an exclusive business arrangement with Human Genome Sciences in the USA, for a 90 day turnaround on novel sequences during which SB will attempt to establish utility for product generation. Merck have objected and intend to create their own sequencing operation making the results public.

We support the SB position in that it differs in no way from research directed towards product generation and wealth creation using any other kind of technology.

1.2 *Are the current policies being pursued by the MRC and other research funding bodies with regard to ethical and social consequences of research in human genetics adequate?*

The Research Councils appear fairly open about ethical issues. The recently formed Nuffield Council which covers genetic research is also another body which reviews ethical questions. In addition, ethical issues are uppermost in the deliberation of the Gene Therapy Advisory Committee (GTAC) in consideration of technical aspects of proposals for gene therapy in patients.

In short, we consider current safeguards in the UK regarding the ethical and social consequences of research in human genetics are indeed adequate.

1.3 *Has the society a right to declare that some research topics should be prohibited because they are intrinsically likely to lead to insuperable moral problems? Should geneticists think more widely than their immediate research goals and their likely consequences or should they leave that to others? Are they pursuing hidden agendas of which the public is unaware?*

The question of whether to declare a moratorium on certain types of research already has a precedent. In 1974, a National Academy of Science study group in the USA called for a moratorium on certain GMO experiments. In the United Kingdom, this moratorium was reviewed under the Advisory Board for the Research Councils Working Party, which recommended that genetic modification techniques should be used with rigorous safeguards. Since then, the regulatory framework governing the use of such techniques has continued to evolve as further scientific information has become available. Today, genetic engineering is routinely practised with the appropriate safeguards.

So, while there may be a precedent for prohibiting certain research topics in the short term, it is questionable whether such practice should be adopted in the long term. When a piece of novel research arises, it should be allowed to continue. Where the ethical or moral issues generally arise is in how that research should be exploited. This is the point at which such issues should be carefully considered. There will be occasional exclusions to this principle, and the best example is direct research on human embryos, where the general population is sensitive to such research.

While it is reasonable to review moral and ethical issues in relation to the exploitation of new technological advances, it should be remembered that when dealing with moral issues, a particular society's moral outlook may change rapidly through time, and if several different countries are involved then it is sometimes difficult to establish a moral "baseline". It is therefore sensible to be flexible in determining a moral viewpoint and arguments in favour of moratorium on germ-line gene therapy should be tempered and left open to future modification at the discretion of any given society. Some of the recent ethical views on germ-line therapy to emerge from the European Council are phrased in terms of an absolute moratorium with little or no room for modification at some time in the future.

However, at this time, since the distinctions between genetic engineering, somatic cell gene therapy and germ line gene therapy are lost on the general public, a moratorium on germ line therapy may actually help build a "responsible" image for the field, without actually damaging or hindering the science too greatly at this stage. Nevertheless, such a position should only be endorsed after a proper evaluation of the science and whether such a moratorium would lead to a likely loss of potential therapeutic benefit.

Some geneticists already think more broadly that their immediate research goals and should be involved in the more general debate on genetics. We do not know of any geneticists who are pursuing hidden agendas at this time. We also believe that the research objectives of commercial companies with interests in human gene therapy are well intertwined.

1.4 *Does research into human genetics lead to a deterministic or any other particular view of human behaviour? Will people try to improve the world through genetic interventions? Should they?*

Research into human genetics does not seem to lead to a deterministic view. General deterministic views assume that given a set of starting conditions, coupled with some general theory or rule of change, then the final outcome can be predicted. This situation does not apply to biological systems, and even more "watered down" versions of determinism, which argue that although we do not know all the starting conditions, or all the laws involved, it is reasonable to assume that the overall system is inherently deterministic, are difficult to prove. Historically speaking, determinism has been more in vogue in the past, and the increasing knowledge derived from genetics has decreased the possibility of a deterministic view precisely because the complexity of interactions between the environment and the genotype makes it exceptionally difficult to predict possible outcomes.

People will inevitably try to improve the human lot through genetic interventions such as gene therapy which generally will be beneficial. However, there is little doubt that genetic intervention could be used for immoral purposes. It does, however, seem wrong to stop all genetic intervention on the basis that some very small minority of researchers may be interested in using genetic interests for immoral purposes that all research in the field should be halted. This is again a question of control of the exploitation of the invention rather than halting the research which leads to the invention itself.

Furthermore, we have yet to elucidate the genetic basis of many quantitative and qualitative phenomena of which behavioural characteristics are an example. It would stretch the most evil of genii to design and experiments to create greater behavioral variation than man is already capable of.

1.5 *Germ line intervention would affect later generations who cannot give their assent. Are there other objections in principle to it which go beyond our limited knowledge of what those effects might be? Would this be playing God? What does that mean and why would that be wrong?*

At this point we know of no objections in principle to germ line modification with the exception of later generations being unable to give their consent. The question of whether or not undertaking germ line therapy is "Playing God" is clearly delineated by a particular person's religious perspective. The more naturalistic equivalent of this has been to argue that germ-line modification is artificial or non-natural. Many of these arguments are reruns of previous debates going as far back as the development of evolutionary theory under Darwin. Several points should be noted:

(i) Genetic diversity is exceptionally high and the mechanisms which continue to generate that diversity have operated throughout the history of life. Both large scale evolutionary changes through substantial genetic change (saltationism) and small-scale gradualistic changes can arise, even in very short time scales. From an evolutionary perspective, germ-line modification in a number of individuals will have no effect on the evolutionary path of human evolution.

(ii) Arguments which assume that even a single genetic modification makes something "artificial" presuppose a background view of the world which dates back to Aristotle and Plato, where objects have an inherent "essence" or "form." Such a view is no longer tenable and the necessary and sufficient properties which define an organism do not require that every organism within a species include every single character trait by which that species is defined. Biological variation is not easily compartmentalised.

(iii) Many of the arguments over whether one is playing God presuppose that there is a line which should not be crossed. For Jehovah's Witnesses, this line is drawn at blood transfusions. Other religious groups draw the line elsewhere. While people's religious beliefs should obviously be respected, similarly such believers should not necessarily seek to force their views on others. In the final analysis, individuals should be free to choose a given therapy in situations where therapeutic benefit will be gained.

There may be aspects of germ line therapy and its effects which are unknown at this time. However, this should not necessarily prohibit such research. If germ line therapy ever becomes available commercially, it is likely to be exceptionally expensive and therefore available only to a very small percentage of the population who can afford it. Furthermore, it is only likely to be developed for dominant negative mutations where the heterozygotes are affected.

Screening may assist in determining whether a couple will have a child with such a defect and it may be possible to screen embryos for such defects. However, in cases where all the offspring are carriers, then embryo selection will not be feasible. There is probably a case to be made for a moratorium on germ-line therapy except in cases where a real benefit can be demonstrated. A voluntary code coming from within the "industry" would look better than one imposed by the legislature and give the general public confidence in the industry.

We believe that instances will arise in which such real benefit is possible. Situations where a deleterious recessive gene arise could be initial candidates for germ line therapy enabling healthy children to be born to

such parents who would otherwise have no child capable of surviving beyond a very young age (e.g., in some complex form of thalassemias the heterozygote recessive exhibits deleterious symptoms).

1.6 *What should the proposed UN declaration and treaty on the protection of the human genome say?*

The declaration should state that the exploitation of genetic information should be for the benefit of mankind. Treatment of disease's clearly a desirable target while the potential for interfering with the genetic propensities of ethnic groups must be explicitly forbidden. An extreme example of the latter might be the elimination of whole groups by inducing infertility.

In circumstances where this is applied to screening and diagnostics, care should be taken to ensure that the medical interests of the individual are put before other non-medical interests such as screening for insurance purposes.

2. PUBLIC AWARENESS AND EDUCATION

2.1 *What is the extent of knowledge of and interest in genetics among different sectors of the public. Should steps be made to improve this and, if so, what form should they take?*

The public perception of genetics is largely based on ignorance. There is a reasonable amount of interest in genetics but the level of understanding of scientific research in this area is very poor. Part of the problem is in how science is reported, with two extremes usually being promulgated—either a "scientist (boffin) discovers a miracle cure", or "scientist involved in killer bug". This two dimensional view of the scientific process is also linked to the generally low esteem in which the general public views scientists. The press often seek to sensationalise a scientific development which means that an unrealistic picture of science emerges. Very rarely is it stated that a "small but significant step was made".

Probably the easiest area to improve information flow on genetics is through improved education in schools.

2.2 *Is there a general anxiety and suspicion about research in genetics? Is it justified or should it be allayed and, if so, how?*

There is a suspicion about science in general. Scientific education in our schools is poor and probably the closest contact people have with science is through programmes like "Tomorrow's World". The general suspicion of genetics is not justified but there is probably more suspicion about genetics than other scientific disciplines as it is less well understood. However, people are generally suspicious of things they do not understand and genetics is an easy target in this respect. The example that most people will recall is eugenic theory in Nazi Germany. The positive aspects of genetic research need to be emphasised, with a focus on what therapeutic benefits can be derived and which incurable diseases may at some stage in the future be cured. This also important from the perspective of health economics where cost containment pressures mitigate against the development of additional "me-too" products and encourage the development of innovative new products which effectively treat poorly met and unmet medical needs.

2.3 *Are there unreasonable expectations of the benefits that might come from genetics? If so, should these be tempered?*

There are no unreasonable expectations about the benefits from genetics. There is, if anything, a healthy scepticism. Manifold evidence is available to illustrate the benefit of applied genetics in the production of food from plants and animals. As the new technology provides us with insight insight into human genetics new benefit will flow, provided that we regulate the application and implementation of the new information in a pragmatic manner.

2.4 *Is there a danger that genetics will be seen as an excuse for socially unacceptable behaviour? Could it be used to justify reductions in social programmes of health, education and welfare?*

There is a danger that a few people will view genetics as an excuse for socially unacceptable behaviour. Such a view is wrong. The nearest position that one could argue for determinism is in single gene disorders, although as discussed above, this is an untenable position. However, genetics should not be used as a tool to justify reductions in social programmes of health, education and welfare. An increasing knowledge of genetics should improve our understanding of the human condition, not reduce it.

2.5 *What are the right questions on the bearing of genetics of human behaviour, ethics and belief?*

A fundamental question which should be addressed is what are the long term objectives of healthcare. Should healthcare be focusing on longevity or quality of life? We believe that health policy in the elderly

and dying should be directed at quality of life, not longevity. In addition, healthcare should also be focused on the very young, particularly where diseases significantly decrease the quality of life or life expectancy of the very young.

We are optimistic that many such possibilities will shortly appear. Treatment of diseases of the central and peripheral nervous system, which seriously impair the quality of life of many young and old people will almost certainly improve as the genes responsible are identified and characterised. In fact, similar benefits will ultimately follow across the whole spectrum of human disease.

3. GENETIC DISEASE

3.1 *How much of genetic diagnosis is conducted as a routine medical service and how much is associated with research programmes? Is the continuity between the two sufficiently well organised? Are some diseases with a known genetic cause not being diagnosed and, if so, why not?*

We don't know.

3.2 *Are there any ethical questions about somatic cell gene therapy which are different from other types of therapy which affect only the patient receiving them?*

There are no new ethical questions introduced by somatic therapy. Somatic therapy represents an extension of conventional therapy and, as a new therapy, will introduce a new spectrum of risks and benefits. From the patient's viewpoint the new agent will be perceived as "just another new drug".

3.3 *Should information about an individual's genome be regarded as confidential or should it be possible for employers, insurance companies etc., to require genetic tests or to obtain the results of previous tests on an individual or their relatives? If not, why is genetic screening testing any different from current medical tests.*

Information about an individual's genome should be treated as confidential information. It should not be possible for insurance companies or employers to have the right to demand access to data. In the United States the question of genetic screening information and its disclosure to employers has been addressed. The introduction of genetic screening programmes for example, by employers, poses many threats to the rights of individuals. In the United States they have not tried to legislate against the use of such genetic screening programmes because of the perceived benefits they may produce. However, they have introduced direct legislative control as to how the results of these programmes can be used. The final decision on whether such data is released should rest with the individual, but provision should be made that non-disclosure by the individual will not result in any disadvantage.

Genetic screening information is different from other types of testing because it gives information concerning the genotype and not the phenotype. Most other conventional tests target the phenotype. Since there is not necessarily a direct correlation between the genotype and the expression of such a genotype phenotypically, it would be insidious to legislate in favour of employers and insurance companies.

The use, by doctors, of knowledge of a patient's genetic makeup for advice on disease avoidance seem wholly desirable. For example, genetic propensity for lung cancer would contraindicate against tobacco smoking.

3.4 *When is population screening for genetic disease appropriate? What factors, such as cost and the availability of counselling and treatment, should be taken into account How should screening be organised and regulated?*

A good example is use, today, of general screening is in cervical cancer. Here the costs and benefits derived from a screening programme can be elucidated along with the appropriate degree of investment required.

However, certain principles should be adhered to when considering screening. First, people should have the right to exercise a choice over screening, i.e., whether or not they wish to be screened under normal circumstances. Second, situations where this may be abused or where other pressures come into play should be prevented. For example, insurance companies may seek to give discounts for people who voluntarily undergo screening. Fourth, screening without counselling is highly undesirable and counter-productive, as past experience with HIV tests shows. Finally, the Government should not insist on compulsory screening although there may be specific circumstances where screening might be promoted where the cost benefit demands are large.

3.5 *If screening for a wide range of genetic predispositions becomes routine, how will people be protected from discrimination on the grounds of their genotype? Should they be?*

People should not be discriminated against on the basis of their genotypes. This would add another level of discrimination and it is certainly unethical to use existing types of discrimination e.g., race, creed etc., as an

argument in support of further discrimination. Protection can only be achieved by keeping the results of the screening confidential.

It seems to us, however, very reasonable to provide screening information to assist the individual to avoid disease and injury as indicated in 3.3 above.

3.6 *Would people be well advised to seek genetic information from sexual partners before the conception of children? Are they likely to? Is this likely to change with future research?*

The search for genetic information on a sexual partner should not be promoted since there is always going to be an ever increasing number of markers available for testing. The types of diseases people have concern over are often rare and it should be left up to individual choice on whether to seek such information. The Government should not give official sanction to such a screening programme or promote it. It is unlikely that the screening of sexual partners will change the direction of future research as the economic benefit of such a programme will not be as great as that of producing therapeutic agents and the chances of liability claims are high.

4 Economic benefits

4.1 *What assistance in the treatment of disease or the design of drugs is given by knowledge of the gene(s) associated with a particular disease?*

A knowledge of genes provides insight into the processes which lead to the development of diseases and therefore suggests new targets for drug development. Genetics will become increasingly important in drug development since it provides information on new approaches and targets. However the downside is that genetic research and in particular, the sequencing of the human genome, is leading to an information explosion which is swamping scientists.

For a wide range of diseases e.g., heart diseases, if the genes involved are known, then it should be possible to screen individuals suffering from heart disease and define the disease sub-set. This will lead to more accurate treatment since a drug's efficacy may be greater in one sub-set rather than another. This may decrease the market volume of a given drug, but will increase the efficacy of particular drugs which are more effective in one disease sub-set rather than another. In other words there will be an increased cost/benefit ratio at the expense of market size.

We see the availability of information to the individual of his or her genetic propensity to disease as an extension of the trend towards health consciousness. Both the individual and the public health system must surely benefit. The example in the United States of the reduction in incidence of cardiac infarct following the understanding of the role of diet as a contributory factor is clear evidence of this welcome trend.

4.2 *Are there differences, in principle or in practice, between gene and conventional therapy? How might these affect development costs? How will this affect the actual cost of treatment?*

The earliest forms of gene therapy required treatment of cells outside the body (*ex-vivo* gene therapy) and have, by and large, been suitable only for blood cells. Very considerable research is ongoing to devise delivery vectors or systems to target genes directly to specific cells and tissues (*in-vivo* gene therapy). Once best become available, the production and delivery of gene therapies will increasingly resemble conventional therapies even to the extent of oral administration in many instances. The interest of pharmaceutical companies lies largely in the possibility that gene therapies will require manufacture on significant scales as with commercial drugs today. Costs of therapy will lie in the same ball park as the successful biotechnology-derived drugs such as Epogen or tPA, but very likely with lasting rather than episodic benefits to the patient.

4.3 *To what extent do factors, such as technology-transfer facilities, patent protection and regulation, influence the commercial exploitation of research findings?*

Factors such as technology-transfer, patent protection and regulation all have a significant effect on the commercial viability of a given piece of technology. Poor mechanisms or technology transfer will mean that either a technology or potential product will not be moved from an academic to a commercial environment rapidly or with sufficient understanding on either side necessary to maximise the chances of success. In the case of patents, the recent attempts to modify the draft Directive on the Legal Protection of Biotechnological Inventions in favour of prohibiting the patenting of different forms of gene therapy is an example where, if successful, the potential for gene therapy research in the UK and Europe will have been seriously undermined. Similarly, if the regulatory framework is too costly and bureaucratic then the development of gene therapy products will be stifled. Commercial exploitation is inevitably going to be expensive and it is probable that before commercial development will be undertaken the party undertaking such development will recognise that

it has the right to commercialise such development, accordingly patent protection will at least initially be the governing factor in the exploitation of the research findings.

4.4 *How does the regulatory regime for genetic-based industry in the UK compare with that in other countries? Is there a danger that investment will be lost to other countries with different regulations or with better venture capital funding potential?*

There is a danger that investment in gene therapy will be lost to overseas competitors. In the United Sates several hundred million dollars has already been invested in gene therapy. The figure is substantially smaller for the United Kingdom. This loss of investment relates to issues discussed in 4.3 on technology transfer, patents and regulations. One other factor concerns funding in basic research in gene therapy. Investment at all stages of the research and development process is essential and such investment will only be forthcoming if the development of the product can be seen to lead to a potential commercial product.

4.5 *What products, other than medical diagnostics and therapies, might be produced as a result of human genetic research?*

The most likely areas where other gene therapy products could be utilised is in the cosmetics and sports industry.

5. Research

5.1 *Why is it worthwhile to map and sequence the human genome? What are the relative advantages of mapping expressed genes only versus completely sequencing the genome?*

There are both theoretical and practical reasons for mapping the human genome. If the aim is to understand the molecular basis of life and even the life process itself, then a knowledge of the human genetic map helps researchers to find their way around. A key question is how complicated are humans. For example how many genes are needed for the human to function properly? This will include a knowledge of how many structural genes, enzyme genes, regulatory genes, etc., are needed. This information will help provide an understanding of how to model biological processes, although the aim of providing a full explanation of biological processes in the human is likely to be hindered by the sheer complexity of the system. With information on the human genome it will be possible to look at different aspects of biological processes in humans.

The most important practical benefit will be to find which particular genes are linked with which disorder.

There are limitations to this exercise. First, it will be describing more complex systems than has ever been done before and having the map will not tell us how the network works. So there will still be a need for an empirical input into drug discovery. Second, one may begin to develop an understanding of what the constraints are in the network, although basic attempts to knock out the function of specific genes, e.g., Il-2 deficient mice, has given unexpected results, such as only a down regulation in activity as opposed to a complete shut down as would have been expected. This information in itself will also be useful in searching for new drug leads.

5.2 *What will it tell us about the human species and the individual that would not otherwise accrue from piecemeal studies?*

The advantage of the human genome project is that it is not a piecemeal study. Piecemeal studies are usually guided by what you expect. On the other hand, a larger more comprehensive study opens up the possibility of looking at different "paradigms" or approaches and is more likely to put the scientist on the path to effective discoveries.

5.3 *To what extent are human characteristics determined by the genome and to what extent does the environment influence the expression of genes?*

The question of overall dominance of either the phenotype or genotype cannot a priori be answered. If anything, it is the phrasing of such a question in the past which has led to the search for a dialectical explanation based on genes vs environment. A more complex approach is needed based on an ongoing continuous interaction between genes and their environment with multiple feedback loops along each step of the way. Genes define the "biological network", although this network is not laid down at birth. Instead, there is constant re-programming of the network by the environment, which acts upon the genetic framework. Developmental processes show that environmental effects can trigger genetic changes at certain times, while at other times no effects are observed. Thus, there is a constantly changing network which incorporates self-correcting processes. Even in identical twins it is possible to detect changes.

5.4 *How much is understood about the organisation of coding information in the genome? Is it conceivable that interventions such as those produced by gene therapy might have unforseen effects?*

Probably less than 50 per cent of the whole story is understood. The role of "non-coding" DNA and the sequences of DNA involved in regulation and control of expression of structural genes is poorly understood, although it is known to be important in defining species differences. The volatility of such sequences will help to determine the species barrier. Non-coding DNA is not significant in terms of gene function, but it probably plays a central role in phylogenetic evolution.

It is conceivable that gene therapy could have unforeseen effects but enough is usually known about the gene units which are the subject of the therapeutic modification. Scientists are becoming clearer about the chunks of DNA which are involved in expression.

5.5 *Is the financial support for research in human genetics adequate when compared with the results which may flow from it?*

Given the overall poor levels of expenditure on research in the UK in general, it is certainly questionable whether there is enough financial support for human genetics. When this is considered in the light of possible therapeutic benefits which could arise from such research, combined with the fact that this is an area in which the UK has been traditionally strong, the case for additional funding becomes overwhelmingly strong.

5.6 *Is the UK a good place to conduct such research?*

We believe the UK has a major role to play in the development of gene therapies. Our intellectual and experimental contribution can be equal, if not better, than those of others, and the overall costs involved are far less than, say, for particle physics.

6. Evolution

6.1 *What evidence is there of continuing evolutionary genetic change in humans?*

The evidence of continuing evolutionary genetic change in humans is seen in examples of sickle cell anaemia and resistance to malaria, and the more recent suggestion that cystic fibrosis incidence is linked to cholera.

6.2 *What may be the consequence of modern social organisation for human evolution?*

Technological and social adaptation are occurring at an ever increasing pace and will tend to dominate natural selection. Evolutionary change will therefore be dampened. If one could measure evolution over thousands of years, then social change will instigate selective pressures. Traces of selective pressure in progress can be found in various allelic distributions of particular genetic traits.

6.3 *What may the consequences of environmental change be for human evolution?*

The most likely outcome will be that environmental changes will have less effect on human evolution due to technological developments. However, if there were significant or extreme environmental changes, e.g., climatic, geological, then these could affect human evolution.

6.4 *What may be the consequences of the pursuit of scientific knowledge for human evolution?*

The pursuit of scientific knowledge will probably reduce the rate of evolutionary change. However, the processes involved in evolution are complex and generated over long time scales, so to identify specific changes is impossible. Several authors have discussed the possibility of units of cultural evolution mirroring genetic evolution and that such units would be involved in human evolution. There is no evidence to support this.

6.5 *What might be the evolutionary impact of selective fertilisation or termination and of other forms of extreme discrimination?*

It would probably be difficult to practice these selection strategies on a wide enough scale to have any effect. These attempts would be a "pinprick on evolution".

6.6 *In what ways does manipulation of the germ line in the clinic or laboratory differ form natural variation?*

Natural variation is defined as random variation which arises due to the normal processes of mutation. Germ line manipulation, although not arising as a result of random changes, constitutes one possible change amongst

many others. Natural variation or variations based on human intervention will still be subject to the same selective pressures. It is just the precision of the change which is being affected, which in turn will reduce the likely timescales for these changes to arise. However, it should be understood that human intervention will not lead to a complex of deterministic changes, because background natural variation is still taking place. Germ line modification in evolutionary terms is an extension of artificial selection, an activity which humans have been pursuing for thousands of years.

6.7 *Human evolution has been driven by sexual reproduction guided by human behavioural drives. Should clinical interventions be allowed to interfere with this process?*

No. Clinical interventions should not be allowed to interfere with this process.

Memorandum from Professor John Sulston and Dr David Bentley, The Sanger Centre (HGC74) (16 December 1994)

GENOME RESEARCH IN THE UK

Why sequence the human genome?

The DNA sequence that comprises the human genetic code, holds all the information that is necessary to determine the correct structure, function and development of the organism. To determine that sequence in its entirety will therefore provide the means to understand the control of all complex biological processes, the components that take part in them and the cause of aberrations which cause abnormality or disease. Genetic factors are now widely recognised to be important in the majority of diseases including the most common ones, i.e., cancer, heart disease, diabetes, etc., and the sequence of the human genome will therefore have a particular impact on health care. Further, to obtain such a complete understanding at a new level, will provide the opportunity for the development of many novel therapeutic agents, possible using previously unrecognised approaches. In contrast to all other biotechnologial approaches, the entire DNA sequence is *accessible* and it can be determined *now.*

The pace of work in human genetics is accelerating rapidly with the realisation that the current technology will provide us with an economical way of determining the ultimate map of the genome at the sequence level in a finite time and with finite resources. To achieve this ambitious goal will require the maximum co-ordination of a truly international collaborative effort, with sufficient funding from a number of centres and the common agreement that the basic sequence information will be in the public domain. We are particularly fortunate in the UK as the long standing of UK scientists in human genetic research has provided an excellent foundation for the current work. Therefore we are in a privileged position to play a major part in this programme, given sufficient funding is made available. It is this realisation which has resulted in the creation of a genome campus at Hinxton with the Sanger Centre (jointly funded by the Wellcome Trust and MRC), the MRC Human Genome Resource Centre, and the European Bioinformatics Institute. This campus will provide an excellent and rapidly growing focus for much of the work directly aimed at determining the human genetic code.

What is required to maximise the success and the benefits of the UK's lead in the international programme/in both a national and international context.

Funding

It appears that international funding for the human genome project is increasing rapidly, and it is important that the UK maintain its position in this field.

Data availability

The sequence of human DNA should be released immediately as it is determined, into the public domain and should be freely available without license/patent protection. Making the information accessible to the entire scientific and industrial community ensures the best use and further development of knowledge arising from the sequence from a variety of perspectives. However inventions arising from these downstream developments may be protected in the usual way.

Commercial developments

It must be clearly recognised that there is the potential for the development of new lines of therapeutic agents or reagents, which benefit human health. The downstream development of each of these products from the DNA

sequence will require a tremendous investment and it is appropriate that such an investment is provided by pharmaceutical and related companies. This work should be adequately protected to ensure returns on such investment. At the same time the form of protection must not compromise other research in the public domain arising from the DNA sequence.

Awareness

There is a need to promote greater awareness in the society as a whole of the importance and value of such information as it emerges. To promote such an awareness requires a much greater emphasis on public education, particularly in science at the primary as well as the secondary school level. This in turn, prepares the way for passing on current information through the media. Greater knowledge of the subject will promote better understanding and debate of the issues in an informed manner and should allow the optimal conclusions to be reached.

Decisions

There are already many guidelines in place for the handling of sensitive clinical and other personal information and these should serve as a basis for dealing with sensitive issues arising from DNA sequence information. Decisions on policies should be the joint responsibility of specialists in Genetics, Counselling and related sociological areas, and members of the general public.

To enable the general community to play a full role in such decision making, it is important that they have the benefit of the maximum available information.

Letter from Professor Lewis Wolpert, Department of Anatomy and Development Biology, University College London Medical School (HGC75)

I am replying in a personal capacity to the request for comments. I wish to make just three points.

(1) There seems to be a disproportionate concern about the possible impact of new knowledge about human genetics. Many of the supposed ethical issues are not new even though there may be particular problems relating to privacy, insurance and patenting. It is hard to see how the problems of somatic gene therapy differs from any new medical treatment or why information from genetic screening should be treated in a manner very different from other prognostic medical examinations, like those for heart disease or cancer.

I would urge the Committee to test any proposed regulatory mechanisms against other "unregulated" processes in medicine, and those social factors that affect individuals and families. For example, there is already, it seems, many regulations affecting assisted reproduction while individuals are free to pursue unassisted reproduction without restraint.

(2) It is very important to distinguish between science and technology; or more specifically between our scientific understanding of genetics and its application. It is worth recalling that doctors are, in general, not scientists. Thus if controls are envisaged then this distinction between science and technology is essential. For, genetic research, provided that it conforms to standard ethical procedures, should only in very exceptional circumstances be constrained, as in the current legislation relating to research on human embryos.

(3) Public involvement in any decisions involving the use or control of genetics is essential. This will require both public debate and efforts to make the public more gene literate. Research will be required to understand not only public views, but also how much knowledge or appreciation of genetics they have. In the long run people should be as free as possible to make their own choices with respect to both genetic information and related treatment.

Memorandum from the British Medical Association (HGC76) (20 December 1994)

GENERAL ETHICAL AND REGULATORY

1.1 *What do we need to know about the way genes work in order to make decisions about the use or regulation of genetic information? Are we likely to obtain this information?*

In regulating any technology a thorough understanding of the scientific, ethical and social issues and their implications is required. Legislators must also take account of how regulation of one sphere of technology or of one type of data might set precedents for others.

In the field of genetics, information about the way the technology will be used is as important as understanding the way genes work in assessing what, if any, regulation is required. As our understanding of the relationship between genes and disease processes develops so the potential for abuse will increase. For example if employers began using genetic screening unjustifiably to exclude potential employees from the workforce or if insurance companies used the technology inappropriately to determine policy premiums, these would be areas requiring some form of regulation. There is also the potential for misuse of techniques such as DNA fingerprinting. The police have suggested in the past that a DNA sample should be obtained from every man in the country in order to help capture rapists, murderers and other criminals. However, there are considerable concerns about such information being used for other purposes and the BMA cannot support such a register at the present time. If such a register were to be kept in the future, careful regulation would be needed to avoid abuse.

Any regulation should be conducted in an open, democratically accountable and representative fashion. The views of different interest groups including legislators, ethicists, scientists, health and environmental experts and the general public should be take into account. In doing so, however, undue weight should not be given to the views of particularly vocal minority groups.

1.2 *Are the current policies being pursued by the MRC and other research funding bodies with regard to ethical and social consequences of research in human genetics adequate?*

In 1992, the BMA recommended that scientific bodies, including the research councils, but also the Royal Society and co-ordinating centres such as the Human Genome Project, devote greater resources and efforts to consideration of the ethical, social, and environmental implications of developments in this field. The BMA also recommended that central government should increase the funds available for pure research in the field of human genetics. This will have the effect of broadening the research base and will reduce the influence of private companies, particularly pharmaceutical companies, which have a financial stake in promoting developments in a particular area. All research in this area should be assessed by an independent ethics committee. It is also important that the ethical and social consequences of the research are considered before the techniques are implemented rather than regulation following the practice.

1.3 *Has society a right to declare that some research topics should be prohibited because they are intrinsically likely to lead to insuperable moral problems? Should geneticists think more widely than their immediate research goals and their likely consequences or should they leave that to others? Are they pursuing hidden agendas of which the public is unaware?*

Society has a role in ensuring that scientific research does not overstep the boundaries of ethical acceptability. Time must be given for reflection to ensure that issues such as human rights and justice are not forgotten when scientific advance becomes the sole ideal. As knowledge develops concerns are raised about how new technology will be used. Society has a legitimate interest in ensuring that research remains within acceptable limits.

Geneticists have shown commendable caution in their research, allowing time for consideration of the social and ethical implications of their work. The BMA would like to see more self-regulation of this type among scientists and the establishment of consensus guidelines by the scientific bodies. A continuing willingness to discuss their work openly will help to dispel any unfounded fears of scientists pursuing hidden agenda.

1.4 *Does research into human genetics lead to a deterministic or any other particular view of human behaviour? Will people try to improve the world through genetic interventions? Should they?*

People are more than the sum of their genes. The inheritance and expression of most traits are not based on a simple Mendelian genetics. Many genes may interact with each other and the environment to produce a particular phenotype. This should not be forgotten.

The BMA believes that biotechnology and genetic modification are in themselves morally neutral. It is the uses to which they are put which create dilemmas. The challenge is to try to maximise the benefits of genetic modification and minimise the harm. Using the science of genetic modification to select children with particular physical, emotional or intellectual attributes is unacceptable. However, if trying to "improve the world" includes alleviating suffering and severe genetic abnormalities, without compromising the status of people who already exist with those abnormalities, then this a worthwhile goal.

1.5 *Germ line intervention would affect later generations who cannot give their assent. Are there other objections in principle to it which go beyond our limited knowledge of what those effects might be? Would this be playing God? What does that mean and why would it be wrong?*

The effects of germ-line gene therapy do not die with the individual but are handed down to all future generations thus breaking completely new therapeutic and ethical ground. The BMA takes the view that at

present, germ-line gene therapy is unacceptable and any advances in it should only be made when there is sufficient knowledge of its possible implications.

The long-term consequences of germ-line gene therapy are impossible to foretell. Knowledge of disease genes and why some persist in the population at greater frequencies than others is till too limited for us to be confident that efforts to eradicate these genes will be of long-lasting benefit to future generations. It is possible that genes which are eradicated may have potential value which would be lost. For example, it is now well known that the gene for sickle cell anaemia, which is particularly prevalent in tropical Africa and the Mediterranean, protects carriers from malaria.

Another argument against germ-line gene therapy focuses on the inheritance of errors. If during the process of germ cell modification a serious error should occur by, for example, inserting a gene in the middle of another gene and disrupting its expression, this error would be handed down to all the descendants. Because the modification occurs on a microscopic scale such an error could go unnoticed. The error may not even manifest itself during the life-time of that person, if it is a recessive mutation, but only appear years hence as a homozygous trait in the descendants. Unless gene therapy can be shown to be absolutely accurate in inserting and targeting new genes, the potential hazards of genetic modification in germ cells are too serious to permit its use.

It is also debatable whether germ-line gene therapy is actually necessary. There are other simpler techniques which can be used to prevent a disease-causing gene from being inherited such as preimplantation diagnosis. By testing embryos for certain diseases, in vitro, only the healthy ones can be selected for implantation. This involves no direct tampering with the embryo's genes and so avoids the risk of genetic mutations caused by gene insertion. There will be a few couples for whom preimplantation diagnosis is not appropriate. For example, if two people with a recessive disease, such as cystic fibrosis, decide they want children, all embryos will be affected because each parent has no normal alleles to pass on to them. For these couples, alternatives such as gamete donation might be a suitable option. It is arguable whether germ-line gene therapy would be justifiable even for those few couples.

The BMA's current objections to germ-line gene therapy are practical rather than strictly ethical in nature. If the practical difficulties could be overcome and gene therapy were found to be safe, a debate would be needed about whether there are any specific *ethical* objections to this type of therapy.

1.6 *What should the proposed UN declaration and treaty on the protection of the human genome say?*

The BMA does not have policy on this issue. This will need to be widely debated.

PUBLIC AWARENESS AND EDUCATION

2.1 *What is the extent of knowledge of an interest in genetics among different sectors of the public. Should steps be made to improve this and, if so, what form should they take?*

Society's understanding of genetics is still quite limited but there is growing interest in the media and increasing numbers of educational programmes on the subject (e.g., Professor David Suzuki's excellent series last year). Whilst the level of public understanding about genetics is increasing there is still room for improvement. The BMA would encourage medical and scientific experts to work with schools, colleges, universities and the various media to bring to the attention of the public the scientific, social and ethical implications of genetic modification. It is essential that education should be widely available in a way that people can understand and that society as a whole becomes involved in the decisions about how genetics is to be applied. In the USA town meetings were held to inform people about the Human Genome Project and to solicit opinions on the social and ethical issues it raises. Interest groups such as the Genetic Interest Group and PROGRESS can and do play an important role in this country in informing the public about genetic disease and research.

As well as informing and educating the general public about these issues, doctors and other health care workers require better training in the science and ethics of genetics. The 1990 Royal College of Physicians Report on "Teaching Genetics to Medical Students" revealed much scope and many options for improvement. The average number of hours of timetabled genetics in the clinical courses of UK medical schools is only about five and a half. This is inadequate to cover fully such a complex subject. The BMA considers that the science and ethics of genetic modification, the principles and methods of genetic counselling, and the implications of genetic disease should be included in examinations and post-qualification education should be encouraged.

2.2 *Is there a general anxiety and suspicion about research in genetics? Is it justified or should it be allayed and, if so how?*

People's lack of understanding about genetic modification has, in the past given rise to fear and opposition to new developments. These fears are largely unfounded but adopting a paternalistic or secretive approach to the

work is not the answer. The scientific community has a duty to inform the general public of new developments in a manner comprehensible to lay people. Such attempts to educate the public and present an open and accessible work programme will help to avoid images of scientists carrying out clandestine work. The media, through TV science programmes in particular, can be very useful in this context. However, where negative language and images are used such as "Brave New World", this tends to increase anxiety and suspicion.

2.3 *Are there unreasonable expectation of the benefits that might come from genetics? If so, should these be tempered?*

Genetic research is able to offer hope to many people whose family have a history of genetic disease and who themselves may be afflicted with serious genetic handicap. While there is much cause for excitement people should not be given false expectations. Through education, expectations should be kept to a realistic level to avoid disappointment, disillusionment and added distress. It must also be remembered that information alone may not change the behaviour of affected individuals.

2.4 *Is there a danger that genetics will be seen as an excuse for socially unacceptable behaviour? Could it be used to justify reduction in social programmes of health, education and welfare?*

Genetic technology should be used solely to benefit individuals and couples, to help them make choices about reproduction and therapy, employment, insurance, etc. To use genetic knowledge to justify state intervention in individual choice, such as compulsory screening, or to reduce social programmes or funding would be a dangerous and unacceptable development. People should not be discriminated against on the basis of their genetic make-up and every support should be given to those who find it difficult to participate fully in society because of some genetic disadvantage.

2.5 *What are the right questions on the bearing of genetics on human behaviour, ethics and belief?*

The progress of genetic knowledge, while creating some new ethical dilemmas, seems largely to magnify existing ethical problems in medicine. Many, for example those concerning privacy and disclosure, place long-standing unsolved dilemmas of medical ethics in a new context.

GENETIC DISEASE

3.1 *How much of genetic diagnosis is conducted as a routine medical service and how much is associated with research programmes? Is the continuity between the two sufficiently well organised? Are some diseases with a known genetic cause not being diagnosed and, if so, why not?*

This question should be addressed by those working in the field.

3.2 *Are there any ethical questions about somatic cell gene therapy which are different from other types of therapy which affect only the patient receiving them?*

The BMA sees somatic cell gene therapy as no different from other routine and widely accepted therapies such as organ transplantation. As such it raises no new ethical issues but, as with any other new innovative therapies, ethical considerations regarding the testing of these therapies need to be addressed. For example, there must be extensive preliminary research to assess both the potential benefits and risks of the experimental treatment. To be accepted for testing on people, the benefits of the treatment must clearly outweigh the risks. The severity of the disease will also be an important factor in judging whether the risks justify the tests. For a relatively mild affliction, one would be cautious about testing a new therapy that might have unforeseen side-effects because these might be more severe than the suffering caused by the disease itself. On the other hand a patient with a severe or life-threatening disease is likely to be more willing to try out a new treatment, whatever the risks, because he or she would have less to lose. The report of the Clothier Committee addressed these issues and its recommendations have now been accepted and implemented. The Gene Therapy Advisory Committee is charged with the task of overseeing developments in somatic cell germ therapy and the BMA supports its role.

3.3 *Should information about an individual's genome be regarded as confidential or should it be possible for employers, insurance companies, etc., to require genetic tests or to obtain the results of previous tests on an individual or their relatives? If not, why is genetic testing any different from current medical tests?*

In general, and in line with all precedents in medical ethics, genetic information about an individual should be confidential, unless disclosure to third parties has been specifically authorised by the person to whom the information relates. There are a few exceptions to the rule, such as if the law requires it or where there is an

overriding public interest such as might occur in a serious criminal investigation, but generally there will be few circumstances where the release of genetic information on an individual without his or her consent is justified.

Information learned about one family member in relation to a genetic disease may have profound implications for other family members. If the individual refuses to discuss the issue with relatives then any breach of confidentiality without consent would have to be justified on the basis of the severity of the disorder and the implications for other family members. Counselling will be required to inform family members of the importance and implications of conveying the information to relatives. The BMA agrees with the Nuffield Council on Bioethics that there is a need for further debate in this area and that guidelines should be prepared to help those professionals making difficult decisions about whether confidentiality should be breached.

Genetic screening for employment and insurance purposes raises different issues. Screening for employment purposes must be optional and should be offered purely to inform current or prospective employees about the health risks they may run if they are employed in particular types of work. There are, however, concerns that genetic screening may be carried out inappropriately by employers in order to exclude people from employment who are shown to be genetically susceptible to occupational diseases. The reasons for doing so are clear—the costs to companies of hiring people who may become ill are considerable. There will be a loss in productivity due to absenteeism, workers will require sick pay and temporary workers will need to be hired. There are also concerns that because particular genes often occur in greater or lesser frequencies in certain racial or ethnic groups the testing for these genes will lead to the exclusion of a disproportionate number of workers of a particular racial or ethnic origin from certain industries.

Employers may also wish to screen for genetic susceptibility to the major killer diseases such as cancer and heart disease, although the mere presence of a "bad" gene does not necessarily mean that a person will be more susceptible to certain workplace hazards and more likely to become ill. However, an individual tested as being susceptible to any of these diseases may find himself or herself excluded from a whole number of jobs as employers turn him or her down as an economic risk.

Genetic information in the hands of employers who are not sufficiently well informed to judge the significance of the information may have serious repercussions for the work force. The BMA therefore recommends that the use of genetic screening in the workplace should move forward only very slowly and with appropriate regulation and should only be adopted as it is proved that certain genotypes really do predispose individuals to some occupational illnesses. Participation in screening must be optional and the results should not be used to exclude individuals from employment but to inform their own decisions.

Insurance companies are increasingly considering using genetic tests to assess the risk of potential policy-holders. However, as mentioned above, there are problems with the interpretation of test results which might lead to unjustified discrimination against people seeking policies. For example, there have been instances of people with the gene for phenylketonuria being denied health insurance. As this disorder can be treated simply and successfully in early childhood the risk to an insurance company of expensive claims from a policy-holder with the disorder is minimal. An individual with a genetic predisposition to cancer or heart disease is not inevitably destined to become ill with that disease. Factors such as diet, exercise and smoking play an important role in the development of these diseases. Therefore to deny a person insurance or to ask for a very high premium merely on the basis of a positive genetic test result without taking other factors into account would be unjust.

The current practice of insurance companies is to ask prospective clients whether they have information about any problem which is likely to affect their health. This being the case, anybody who had been given a positive result in a genetic screening test would be bound to disclose this information or risk any subsequent claim being denied. The BMA does not feel, however, that insurance companies should be able to oblige people to have screening tests as a condition of health insurance.

3.4 *When is population screening for genetic disease appropriate? What factors, such as cost and the availability of counselling and treatment, should be taken into account? How should screening be organised and regulated?*

Genetic screening has been taking place in a limited way for many years. Since the 1950s most babies born in the UK, and in many other countries, have had their blood tested to establish whether or not they have inherited from their parents the genetic defect responsible for phenylketonuria (PKU). More recently it has become possible to diagnose prenatally the genetic conditions responsible, for example, for Tay-Sachs disease, Huntington's disease, Duchenne muscular dystrophy and cystic fibrosis.

Some see genetic screening as promising a healthier, happier and safer future, while others believe it to be unnecessary, undesirable, and pointlessly extravagant. The BMA's view is that genetic screening can play a valuable role in promoting public health, but controls and guidelines are required to ensure that it is carried out in such a way as to optimise the balance of benefits against risks.

Some genetic defects are particularly prevalent in certain sections of the population and targeting screening programmes at these groups has some merit. However, two examples of this kind of population screening will

illustrate some of the advantages and disadvantages. During the 1970s approximately a dozen American states passed laws requiring that black people submit to genetic testing for the sickle cell trait. The laws disregarded the need for genetic counselling services and for protecting the confidentiality of the test results. They also paid little attention to the problem of inadvertent discovery of non-paternity. The programme was so ill-conceived that carriers of the trait were often left with the impression that they had the disease. Most importantly, because the focus was on a minority, racially oppressed group, the black population felt that the screening was merely a devious way to discourage black people from having children. By contrast, a screening programme for Tay-Sachs disease was set up by Ashkenazic Jews in the early 1970s. Approximately 25,000 Ashkenazic Jews are tested annually in the USA, and the incidence of Tay-Sachs has been reduced by 90 per cent compared to the period before such screening was introduced. The success of this programme was largely because of the initiative came from within the Jewish community and was combined with sophisticated genetic counselling and public education.

The issue of genetic counselling is crucial to genetic screening programmes.

A clear distinction must be made between being a carrier of a genetic disease and either being afflicted by it or having a predisposition to it. Before introducing screening the possibility of false negative or false positive test results should be minimised, although there is always a residual risk which couples should be warned of. Counselling should be non-directive and should be provided both before and after the test, to explain the purpose of the test and the meaning and the implications of the test results. Such counselling is essential for helping individuals and couples to understand their choices and exercise them in a way with which they are comfortable.

The timing of screening can also be a difficult decision. There is no obvious benefit to children of carrier screening and the BMA considers that they should not be tested until they are of an age to understand the meaning of the test and give their valid consent. Many women are given screening in antenatal clinics although it might be more appropriate to screen before pregnancy so that the results can be taken into account in deciding whether to have children.

Another question frequently raised is whether screening should be offered for diseases for which there is no known treatment or cure—the so called gap between diagnostic and therapeutic techniques. The advantage of the former is that it allows the individual to make informed decisions about the future and whether to have children. Debate is currently ongoing about whether to test all new-born boys for Duchenne muscular dystrophy, for which there is no cure. One of the advantages of early screening is that it warns parents of the risk of recurrence in subsequent children and enables them to take preventive measures if they wish. In addition, potential carriers in the family can be informed of the risk. The knowledge would also avoid a delay in diagnosis and the corresponding anxiety for the parents and would enable the parents to prepare themselves for the future, such as modifying their home to accommodate a wheelchair.

There are also disadvantages. Parents are told that their son will develop a fatal condition for which there is no cure, years before the first symptoms appear. The stresses imposed by this knowledge could be profound and family relationships may be put under strain. Further discussion of the ethical issues about genetic screening of children can be found in the recent report of the Clinical Genetics Society which the BMA found to be sensible and broadly acceptable from an ethical viewpoint.

The decision to offer population screening for a particular genetic disease will depend upon a number of factors including the severity and incidence of the disease and the likelihood of curing the disease.

Genetic screening, whether carrier, diagnostic or pre-natal should always be accompanied by non-directive counselling. It should be on a strictly voluntary basis (an exception would be screening children for PKU) and confidential. People should be free to refuse screening without jeopardising either their rights or their children's rights to subsequent care or state benefits.

National screening programmes should be established only for diseases where treatment, or termination in the case of pre-natal screening, is available or where a positive test result will give people information on which to base life-changing decisions such as whether to have children.

3.5 *If screening for a wide range of genetic predispositions becomes routine, how will people be protected from discrimination on the grounds of their genotype? Should they be?*

As with all medical information, an individual's genetic information should remain confidential (see above discussion).

3.6 *Would people be well advised to seek genetic information from sexual partners before the conception of children? Are they likely to? Is this likely to change with future research?*

Those with a family history of a particular genetic disease may wish to clarify their own status in planning their own future. However, this decision must be made by the individual concerned and must be a free and informed choice.

Memorandum from The Dystrophic Epidermolysis Bullosa Research Association (HGC77)
(16 December 1994)

The Dystrophic Epidermolysis Bullosa Research Association (DEBRA) is delighted to be able to contribute to the Science and Technology Committee's enquiry. We are the national voluntary organisation working with people with Epidermolysis Bullosa, a genetic condition in which the skin and mucosal surfaces of the body blister at the slightest trauma. In its most severe forms the condition is very handicapping and, in some forms, is fatal in early childhood.

We have limited ourselves to responding to two sections of the questionnaire.

GENETIC DISEASE

3.1 It is difficult to envisage general genetic diagnosis being conducted in the short term as a routine medical service. However, as more information is obtained in relation to specific diseases, routine diagnosis becomes a possibility in those cases. It has to be remembered that many of the genetic diseases arise either as spontaneous mutations or are recessive and remain unseen until the carrier meets a partner who also carries the defective gene. The more serious forms of Epidermolysis Bullosa (EB) tend to be recessively inherited and it is probably more productive to think of pre-natal diagnosis being offered to couples known to be at risk, i.e., those people who have already had a child with EB or are the siblings of parents of an EB child.

3.2 We do not believe that the issues surrounding somatic cell gene therapy are qualitatively different from those relating to other types of therapy.

3.3 EB is a condition of early onset and so the fact that someone has the condition will be evident without genetic testing. However, confidentiality of information relating to the individual is important in principle and we would wish to endorse this. The Genetic Interest Group, of which DEBRA is an active member, is in the process of developing a policy paper on the implications of genetic knowledge in employment and insurance matters which will be submitted to the Committee.[1]

3.4 Genetic conditions, such as EB, which are rare are likely to be candidates for population screening. Any screening process must be accompanied by appropriate counselling.

3.5 Again, since EB is evident at birth in most cases, we do not feel that this is a major issue for us and our concern is to ensure that people who have the condition are protected from discrimination by legislation. In those late onset conditions where screening may detect abnormality pre-symptomatically we believe that people in this position should receive the same protection in law as will be afforded to people who already have a disability.

3.6 The decision whether to seek genetic information of sexual partners prior to conception will always be a matter for the people concerned. Our experience is that people who may be carriers of EB, such as the siblings of a couple with an affected child, are keen to determine whether they and their partner are carriers of the recessive gene, although such a test is not currently available.

RESEARCH

5.1 It must be worthwhile to map and sequence the human genome because so much information of which we were totally unaware is coming out of this project. Mapping only expressed genes would certainly be helpful but it would not complete the answer to many questions about the nature of the functions of the cells of the human body.

5.2 Piecemeal studies will take much longer to put together in the absence of a more systematic study of the human genome and may give rise to incorrect reasoning.

5.3 In the case of EB, environment plays no part in the expression of the gene. It is, of course, true that a better environment will make for a healthier human being but this is not related to the genomic pattern of the individual.

5.4 The possibility of unforeseen effects as a result of genetic interventions cannot be discounted. However, since many genetic conditions, including EB, are so debilitating the unforeseen effect may not be as bad as the actual condition which is being treated. A considerable amount of animal research work has been done in this field and, so far, there is no evidence of problems.

5.5 We believe very strongly that the financial support for research into human genetics is not adequate. Much of the funding comes from charities, for example DEBRA is the main funder of EB research in this

[1] See Minutes of Evidence for 1 February, p. 52.

country and we regularly receive applications for research grants from abroad. A relatively small amount of money could produce dramatic results for our understanding of EB.

On the question of finance, we are worried that it may be difficult to bring potential treatments developed in the laboratory, as a result of work funded by the charity, into general clinical practice. A condition like EB, which affects 3,000 to 5,000 people in the United Kingdom, may have too small a patient base to make it attractive to pharmaceutical companies to develop the theoretical knowledge gained.

Memorandum from Professor W Dunlop, The Royal College of Obstetricians and Gynaecologists (HGC79) and (HGC79A) (20 December 1994)

I apologise that the College has not been able to meet the deadline for response to your letter of 7 November 1994. That letter was addressed to Professor Chamberlain who, as you may have heard, resigned as president two weeks ago. I have now had the opportunity to consult to a limited extent within the College and also with colleagues working in the field of human genetics and a detailed response to the questions that you ask is attached to this letter.

My colleagues and I have been impressed by the appropriateness of the range and depth of questions that the advisers to the Science and Technology Committee have drawn up on the issue of human genetics. We are pleased to note that you are consulting widely because we feel that it would be inappropriate to restrict consultation to those working directly in the field.

While it is possible that completion of the human genome mapping scheme will permit the protection at an early stage in life of individuals predestined to develop genetic disorders (and this could have devastating consequences for these individuals) it is more likely that this information can be used in some cases to modify environmental and other influences so as to minimise the consequences of a genetic inheritance.

A particularly important problem from the point of view of our speciality is the increasing burden of antenatal screening and testing as well as counselling. Pre-marital genetic screening seems unlikely to have a major impact upon the incidence of genetic disease unless there is a major change in the sexual habits of the population. At present large numbers of pregnancies in the United Kingdom are unplanned or of uncertain paternity.

I hope that our comments are helpful to you. Please do not hesitate to contact me for further information if this is required.

1. General ethical and regulatory

1.2 Current policies appear to be directed predominantly by those with a professional interest in the field. The development of an independent body (with appropriate professional input) similar to that provided for the Human Fertilisation and Embryology Authority could reassure the public that the ethical and social consequences of research in human genetics were being responsibly considered by an organisation accountable to government.

1.3 We think it is unlikely that geneticists are pursuing "hidden agendas of which the public is unaware". Nevertheless this is an understandable fear. The establishment of a body such as that described above might help to allay public disquiet.

1.5 Germ line intervention is still at a very early stage in the human. We recommend that research in this area should be supervised by the organisation defined above. It would be sensible to proceed with caution until the consequences of such selection became clearer.

2. Public awareness and education

2.1–2.2 We consider that the extent of knowledge about genetics among members of the public is generally poor. This can lead to inappropriate speculation and anxiety. We are certain that steps should be taken to improve this, both at the level of education in schools and also by the development of appropriate counselling services for those families known to carry genetic disorders.

2.3 We are not aware of any current evidence that eugenics can be used to improve humankind. However, it is clear that genetics can be of benefit to families carrying major genetic disorders where the avoidance of unwanted affected progeny can be facilitated.

3. GENETIC DISEASE

3.1 Regional Genetics Centres offer as a routine medical service karyotyping, the routine diagnosis for approximately 12 single gene defects using molecular genetic techniques and dysmorphology diagnosis on the basis of syndrome recognition. Active research programmes are associated with most centres and continuity between service and research is essential. We do not have information about the overall organisation of this continuity. It seems quite clear that some diseases with a known genetic cause are not being diagnosed because screening appears to be patchy throughout the country as is the availability of genetic diagnosis. Furthermore the ability to investigate families for genetic disease is limited in some areas.

3.2 Somatic cell gene therapy appears to have a significant future in relation to such tumours as breast and ovarian carcinoma. We do not consider that such therapy raises unique ethical issues.

3.4 There is a real danger that overenthusiastic use of population screening could have a major impact on antenatal services. The development of screening techniques without the concomitant expansion of counselling services could lead to a great deal of personal unhappiness and perhaps to public disillusionment. Extra resources would clearly be required for this purpose and for the provision of adequate antenatal services for those pregnancies requiring intervention. Screening should, in our opinion, be evaluated as a potential public health intervention and should be controlled by a governing body such as we have described above.

Memorandum from The Ethics in Biotechnology Group working within the Religious Society of Friends (Quakers) (HGC80) (December 1994)

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SUMMARY

The extremely rapid development of genetic engineering carries enormous uncertainties for good or ill, particularly in relation to human genetics. The prospects for future generations are very difficult to predict. The nature of the evolutionary process itself is being changed for all future time by bringing it into the laboratory

[1] Not printed.
[2] See p. 1.

where biochemical manipulations of genetic material can make almost instantaneous changes with unforeseeable consequences for all eternity. This, surely, is playing God.

Present developments in human genetic engineering are not under adequate regulatory control and accountability because of the speed of scientific discoveries and the enormous commercial forces competing on a global scale to get patent coverage on as many parts of the genetic code as possible. New national and global regulatory controls and inspection systems are therefore urgently needed.

We recommend setting up of a permanent National Biotechnology Commission representative of all the public and other interests concerned, and also a new international authority under the United Nations. This could possibly be a Human Genetics Agency partly modelled on the International Atomic Energy Agency—a fitting parallel since ionising radiation is itself a cause of genetic mutation and the path taken during the history of evolution.

When considering all of this we as Quakers do particularly draw attention to the continuous need to combine reason and emotion with wisdom, exemplified by *The Ethic of Care and Guide Principles,* developed by the Royal Canadian Commission study on *New Reproductive Technologies* published in 1993 under their profound title *"Proceed With Care".*

Introduction

Eve Samson, Clerk of the Committee, in her letter to the Society of Friends asks how we inform ourselves on scientific and ethical issues.

Note on the Society of Friends

The Society's approach to public issues of exceptional importance is based on a three hundred and forty year history of seeking for understanding and truth. There is a long standing scientific tradition in the Society which has included several eminent scientists (e.g., Eddington, Hodgkin et al). The Peace Testimony is central to our tradition and is actively promoted by working for the resolution of conflict at all levels of human society, nationally and internationally.

The Society has many links worldwide, through the Quaker UN Offices in New York and Geneva, the Friends World Committee for Consultation and the Quaker Council for European Affairs (Brussels). This memorandum will be copied to these and other Quaker organisations worldwide.

The way we inform ourselves

This particular Concern on Ethics in Biotechnology was started in 1992 and has developed through the normal process arising from the non-hierarchial structure of the Society of Friends.

(1) The process begins with the involvement of individuals in a specific issue in science education and ethics.

(2) Those individuals with similar concerns initiate small scale networks of like minded Friends for mutual support and education. In this case, a significant number of these are professionally involved in ethics, science and biotechnology including genetics.

(3) The network(s) grow through regional and national meetings and conferences e.g., at Woodbrooke Quaker College.

(4) The Network Concern becomes recognised by regional meetings, the national executive committee and the Agenda Committee for Yearly Meeting of the Society in Britain. This is the final executive authority and is attended by over 1,000 Friends.

(5) The Network and committees will continue to develop the detailed work and extend it through links to Quakers internationally: they may respond in a similar way and bring the matter to their national Yearly Meetings.

How developments in science and ethical issues are addressed

The Network Co-ordinating Group is at stage 4/5 of the above process at present and is responsible for this memorandum. It is very probable that a session(s) on Ethics in Biotechnology will be included in the 1995 Yearly Meeting next May when it is anticipated a corporate statement in the form of a Minute will be issued and made public.

The ethic of care and guiding principles

We are aware of some of the large number of contributions on ethical issues.

In particular we are inspired by the relevance and utility of the "Ethic of Care and Guiding Principles" adopted by the Canadian Royal Commission on *New Reproductive Technologies* in its report PROCEED WITH CARE 1993 (Vol-1 of ISBN 0-660-15359-9).

A contribution to the development of this Ethic was made by one of the Commissioners, Grace Jantzen, who is a member of Friends House Meeting and Reader in the Philosophy of Religion in the Department of Theology and Religious Studies at Kings College, London. She has spoken on this subject to UNESCO and at various national and international bio-ethics forums.

The following is an extract from the report:

> Although there are differences of emphasis among the ethical thinkers from whose work we have drawn, the ethic of care holds, broadly speaking, that moral reasoning is not solely, or even primarily, a matter of finding rules to arbitrate between conflicting interests. Rather, moral wisdom and sensitivity consist, in the first instance, in focusing on how our interests are often interdependent. And moral reasoning involves trying to find creative solutions that can remove or reduce conflict, rather than simply subordinating one person's interests to another. The priority, therefore, is on helping human relationships to flourish by seeking to foster the dignity of the individual and the welfare of the community.
>
> Where intervention is necessary, its aim should be creative empowerment so that, as far as possible, everyone is served and adversarial situations do not arise. At the very least, intervention must, in this view, avoid causing harm to human relationships. The traditional first principle of medicine, non-maleficence (do no harm), is thus applicable not only to medical practice but to intervention in society generally and is made into a positive commitment to empowerment. The concept of non-maleficence goes beyond simply avoiding actions that might cause harm, to taking steps to prevent harm and create conditions in which harm is less likely to occur and beneficial results are the more likely outcome.

To implement these goals, the Commission identified eight principles to be considered when applying the Ethic of Care which are heartily endorsed:

- Individual Autonomy.
- Equality.
- Respect for human life and dignity.
- Protection of the vulnerable.
- Appropriate use of resources.
- Accountability.
- Balancing of individual and collective interests and
- Non-commercialisation of reproduction.

The Working Group feel these principles are consistent with values generally held by Friends and have adopted them as criteria for evaluating issues in their own deliberations.

We note ethical issues are now being considered on a global interfaith basis by the Parliament of the Worlds Religions—See A Global Ethic Ed. Hans Küng which presents the Declaration of this Parliament in 1993. This development is important because it has a wider scope and is consistent with the Ethic of Care and is also relevant to multi-ethnic societies such as those in Britain and other countries.

RESPONSES TO QUESTIONS

General Ethical and Regulatory

1.0 We support the direction of the questions and in particular the implicit recognition that however good the situation can be made in the UK the practicalities and issues are not confined by national boundaries but should be covered by global agreements.

1.1 We need to have the clearest possible understanding of the way genes work if the use or regulation of this information is to be effective. The subject areas include:

- The production of proteins and how this is controlled inter alia by the different ways gene codes can be "read".
- The mutual interactions of some genes.
- Gene multiplication in the laboratory using the polymerase chain reaction.
- Hereditary effects if the germ line is modified.
- The release of genetic material into the biological environment enabling possible transfer of genetic information e.g., the HIV retrovirus, oncogenes etc.
- Mutagenic effects of radiation leading to cancer etc. and hereditary effects.
- Mutagenic effects of chemicals.

— Crossover between species, particularly via the infective transfer by zoonoses.

— Plasmid transfer between bacteria and the environment and between bacteria when some are also zoonoses.

New information on these and other subjects is being obtained at a rapid and increasing rate which is not under effective control.

Long term predictions based on the current limitations of knowledge are unsafe and therefore we urge that regulatory authorities at all levels should—"proceed with care".

We understand that there are particular genes which predispose people to cancers e.g., of the breast. We know more cancers are caused by dietary and environmental factors than by hereditary ones. We question the priorities of public funding policies that enable large sums to be spent on looking for genetic risk factors without increasing proportionately public funds invested in preventative medicine and cleaning up our polluted environment.

1.2 As far as we can ascertain major funding bodies such as the MRC and Leverhulme Trust have not published ethical guidelines concerning genetic research on humans.

The Human Genome Project has a specific set of projects under the heading of ELSI (Ethical, Legal and Social Implications) which has funded a number of meetings. We are unaware of anything similar having been undertaken with UK government funding.

We feel strongly that it must be the task of research funding bodies and the scientists funded by them, to consider the social implications of the research. We have heard it repeatedly stated that most working scientists lack the time, inclination or expertise to evaluate the social implications of their research. This confirms our opinion that geneticists should be required to work within laid-down ethical boundaries and be accountable for adhering to them. We are also concerned that the basis of our health system could fall into the hands of a monopoly of commercial interests. Research policies need to be based on respect, humility and compassion as well as on the need to be profitable.

We should like to know, for example, if supposing social research indicates that most people would rather not know anything about their genetic status, how would this affect the whole dynamic of grant awards to projects and emphasise the potential medical utility of genetic research.

We recommend that a permanent National Biotechnology Commission be established with representatives from non-governmental as well as governmental organisations, industry and academia, the majority of members having public interest/group affiliations.

The Government should also continue to fund research into ways of tackling medical problems without employing the techniques of genetic engineering.

Government must not forget that most medical advances have come through improvements in nutrition, sanitation and preventative medicine.

We welcome the section in the Government's recent White Paper "Realising our Potential" which suggests that research funded by research councils should be subjected to greater public consultation.

1.3 (a) Yes: altering germline cells for eugenic reasons, cloning humans and making animal and human hybrids. We are totally opposed to any genetic research being undertaken to manufacture weapons.

Any restrictions on the democratic freedom to investigate, to ask questions, to challenge accepted notions in public cannot be undertaken lightly. Once that is understood however, any person's research is conducted in the light of constraints: ability, available resources, chances of success, topical interest, moral scruples and the law. Notably in the social sciences making explicit decisions about one's ethical framework is truly a part of the research. Such decisions will be subject to criticism which may lead to them being modified and on occasion regulated, e.g., the Data Protection Act of 1984. We need to develop a research culture across all science and technology which insists on evaluating the ethical framework. Responsible freedom consists not in doing what you like but in being able to justify to what you wish to do. Simply because a technical problem is in principle soluble, does not put individuals or society under any obligation or justification for solving it.

(b) Genetics should not act in isolation but attempt to arrive at consensus regarding their work with those selling, applying, buying, using, regulating or commenting on it. David Suzuki and Peter Knudtson in their book, Genetics, stated: "By venturing into the privacy of human genomes, geneticists are not simply satisfying, as some would insist, their own insatiable scientific curiosities. Whether they recognise it or not, they are also creating new opportunities for others to harness this scientific knowledge—for good or for ill–in ways that will influence the lives of fellow human beings". (Unwin Paperbacks, 1990). They add: "Knowing this, each of us must be willing to do more than simply applaud each startling new breakthrough in molecular genetics that is announced in newspaper headlines". *(ibid).*

Like other scientists, and the rest of us, geneticists need to be fully conscious of how easily science can be used by the wealthy, the powerful the unscrupulous to destroy: whether intentionally or accidentally. We remember with compassion the victims of Chernobyl and Bhopal.

(c) We understand from discussions with working scientists and from published material (e.g., Dixon) that there are some scientists who are pursuing hidden agendas.

The following quotations from the SIPRI Year Book 1994 (page 714) make it seem very probable that genetic engineering is being exploited for military purposes in spite of the Biological Weapons Convention:

(i) "offensive work can be conducted under the guise of defensive preparations . . . since both activities require the same basic know-how and laboratory techniques at the R&D stage".

(ii) "However, proposals to make such activities transparent under national or international control have this far been rejected".

We deeply regret this as we feel it can contribute to fragmentation of scientific collaboration, and accelerate for profit the military or private exploitation of knowledge, techniques and material that should be available to all humanity. In particular we think of the materially poor and marginalised, many of whom live in the economically deprived countries who could benefit greatly from preventive medicine resources, but are unlikely to benefit from the current priorities given to human genetic engineering so far.

1.4 (a) Yes, new knowledge in genetics does contribute to a deterministic outlook unless this is balanced by awareness of the higher complexity of thought and inspiration which many individuals have used to make changes in human society and culture for better or worse. This is exemplified by the practice of religions of love, or religions of hate, e.g., attempts to establish a "Master Race" and the practice of genocide.

A deterministic view of behaviour also under-estimates the powerful influence of "chance" factors on an individual's experience of life. The way people treat one another and relate to their physical surroundings have profound effects on their psychology, spirituality and potential to behave negatively or positively. There is a real danger that too much determinist thinking may weaken our capacity to take responsibility for our own actions as often as we could, "the fault, dear Brutus, is not in our stars but in ourselves".

(b) Yes. The word "improve" is subjective. In the hands of humane scientists we hope genetic engineering might—if appropriate be used to decrease or ameliorate severe suffering. Each case for possible genetic intervention must be assessed according to an agreed, public list of ethical criteria. No intervention should be undertaken until such criteria have been agreed, been publicised and are legally enforceable (see 1.6).

(c) In considering whether people should use genetic engineering to try to improve the world we distinguish between genetic intervention to improve health by better diagnostic or therapeutic techniques, and those that might be for "enhancement" (eugenics), or convenience e.g., the sex of a baby. We welcome the first type of intervention but we are opposed to the second type. We are interested to hear that this has already been banned in France and we urge the British government to do likewise.

A fundamental belief of the majority of Quakers, certainly in this country, is that there is that of God in everyone. We find it difficult to anticipate scientists finding that of God on chromosomes 11 or 15. We are convinced that we humans are infinitely more than an assembly of cells, gene machines, or protein factories as people are sometimes described. We are much more than the sum of our constituent genes.

As a civilisation richly endowed with medical and other scientific knowledge and expertise, we now face the greater than ever risk of viewing people as commodities, to be evaluated according to their utilitarianism, rather than to be loved for their inherent value, regardless of any materialistic benefit to society. We need to treat the social problems that cause discrimination; more than trying to engineer away non life-threatening or debilitating differences. We reject any form of prenatal diagnosis/made purely for socio-economic reasons and which would be merely weighted against the cost of care for the disabled.

It will be contemptible if our civilisation having outlawed so much discrimination on grounds of racism, sexism, disability, sexual orientation, and religious affiliation in this century, now condones and allows to increase discrimination based on genetic variation.

Government must move rapidly and effectively to ensure that this does not occur. The biotechnology industry must not be allowed to continue unconstrainedly in an ethical vacuum, it must be made accountable to a publicly defined ethic and be made legally responsible both for the direction and application of its research. Government policy needs to distinguish between the dubious or undesirable research, and the ethically acceptable and to make known its criteria like other governments such as the French and the Norwegians have done.

1.5 (a) The ethical and social issues relating to the deliberate modification of the germ line and the consequences for the resultant progeny are deeply disturbing for many reasons, which include violation of most of the Guiding Principles of the Ethic of Care, e.g.

— "Individual anatomy" of people to choose how they live their lives would be threatened.

— "Equality" of every member of the community would be disregarded.

— "Respect for human life and dignity" including the unquantifiable value of our connections to past and future generations would be questioned.

— "Appropriate use of resources" would not include funding such work.

— "Accountability" questions whether those with scientific or governmental power are sufficiently responsible to the public who, as of right, should be in overall regulatory control of the direction of science policy and practice which affect the future of their children and following generation.

Further objections are that germ line intervention:

— Could potentially be initiated by a single individual or group of scientists to satisfy their own private motives which could include psychological power play—history gives no confidence that wisdom and responsibility will always prevail.

— If carried out would be forever irreversible once the altered gene(s) had entered the gene pool of the reproductive population.

— Would create a precedent that would make it easier for the proponents of engenics to advance their cause.

— Demand for health services is likely to outstrip availability of resource unless spending priorities overall give more importance to the value of *all* our individual lives. Research to create a "better" or "perfect" human should not draw on their limited resources, such "engenic" practices should be banned as they are in France.

We applaud the policy of the Norwegian government towards people who are disabled:

> *"The Government's primary objective is to ensure maximum participation and equality. . . . and grants a natural and rightful place for disabled people in society ('Biotechnology Related to Human Beings'; Norwegian Ministry of Health and Social Affairs 1993)."*

(b) People's perceptions of God vary widely. Like many others we view ourselves as temporary stewards or custodians of creation. "Creation" is used here to imply an underlying relationship with the spiritual force for good which we call God. Humans have the right and responsibility to act for the well-being of all, including the rest of the animal kingdom, and to minimise opportunities for harm. As Quakers we try to follow Jesus' teaching to love our neighbours as ourselves, believing this is aimed at removing the unjust distinctions, inequalities, divisions and strife among people and nations which are the cause of intense suffering, all over the world.

Germ line intervention is a potential new power to suddenly alter natural life for all time. This, if abused by scientists, the military, or politicians, as power sometimes is, can lead to individuals giving themselves "godlike" powers with consequences that are incalculable.

Germ line intervention could be thought of as one of the "fruits" of the tree of scientific knowledge. If we eat of the fruit of the tree by altering some of the genes, then the people produced will be conscious they are a product, not only of God's natural world but also of manipulations in the science laboratory.

This would be a new difficulty for people facing the questions "who am I?", or "what is the meaning of my life?". These are profound challenges for the intellect, emotions and spirit for which answers have been sought since the dawn of consciousness. This search could only be made much more difficult by introducing germ line intervention into human evolution and thereby reinforcing a reductionist mechanistic view of the meaning of life.

(c) With the knowledge available to us both of the nature of the technology and of the human capacity to manage life wisely or unwisely, we believe it is wrong to use these God-like powers before much further thought has been given.

We urge the government to facilitate and fund an Ethics Forum for vigorous national discussion concerning the values behind and the reasons for the impetus to reprogramme the human germ line. In the meantime it should declare a moratorium on any experimentation until some greater consensus about ethical boundaries has been achieved and published.

"O, wonder!

How many goodly creatures are there here!

How beauteous mankind is! O brave new world that hath such people in it"

(The Tempest)

Is it to be Miranda's or Huxley's Brave New World?

1.6 (a) We believe the proposed UN declaration and treaty on the protection of the human genome should address ethical and material issues relating to:

(1) Equality of care for this and future generations.

(2) Individual autonomy and respect for human life and dignity.

(3) The accelerating pace of research unrestrained by agreed, publicised ethical guidelines and regulations.

(4) An international legal framework for open access to the patented information on the human genome and which might be extended later to cover the genome of other animal and plant species.

(5) Medical research and medical treatment.

(6) Commercial forces including personal insurance and patents, and the balancing of individual and collective interests.

(7) The possible misuse of knowledge e.g., for military purposes (attempts to establish a "master race" could be more successful now than in the past).

(8) Verification of compliance, nationally and internationally.

(b) It has been suggested that the effects of genetic engineering may be more far reaching than those from nuclear fission and fusion, and the associated ionising radiation, cause of mutation both somatic and germ line through out the history olf life on earth.

It is therefore very appropriate to consider the complex task of preparing a UN Human Genetics Declaration and Treaty by drawing on relevant experience in the parallel fields of the work of the International Atomic Energy Agency (IAEA). This special agency of the UN, has been addressing many of the issues listed above for the last 38 years and is widely respected. David Fischer, former Assistant Director General of the IAEA is prepared to give oral evidence on the IAEA.

The relevance of the IAEA is that its statute authorises the Agency among other objects;

(1) To act so as to support the purposes and principles of the United Nations to promote international co-operation.

(2) To assist research for peaceful uses.

(3) To foster the exchange of scientific information.

(4) To consider the needs of underdeveloped countries.

(5) To establish and administer safeguards to prevent military applications.

(6) To submit reports to the UN General Assembly, the Security Council, the Economics and Social Councils, and other UN organisations if required.

(c) We propose, that the UN Declaration and Treaty should include the following:

(1) The setting up of a new United Nations Human Genetics Agency, especially to cover the issues outlined above, and below.

(2) A requirement that all sequences of the human genetic code of any length whatsoever shall be kept in the public domain in a way that supersedes any existing patent control by individuals, groups or corporate bodies.

3. (a) That, because the human genome project has progressed faster than expected when the original "open" information policy was made and a large part of the genetic code has already been subject to patent applications, it is essential that "open access" to this information and the right to use it shall be re-established immediately, subject to compliance with a code of restrictions (see 4).

(b) This could be done by setting up under the new UN Agency a World Patent Licensing Office to supersede the existing conventional patent licensing system currently applying where there are patents on parts of the human genetic code. The new UN World Licensing Office would issue, as of right, licenses to use existing or future patents to all applicants—subject to 4.

(c) The applications should be registered and the licenses issued for a small standard administrative fee.

(d) Royalties to the existing Patent holder should be paid but limited so as not to restrict the commercial applications (e.g. to a maximum of say 5 per cent of any net profits accruing from use of a patent).

4. That the use made of the genetic information should be reported annually to the new UN Human Genetics Agency and its use monitored in selected cases to ensure that only purposes which comply with the Agency Code of Practice (to be formulated, outlining agreed legitimate uses) are pursued.

5. A verification inspection system should be established which is modelled on those for the Chemical Weapons Convention and the Biological Weapons Convention. Expert advice can be had from the Verification Technology Information Centre (VERTIC) which has wide experience of these issues in many different military and peaceful contexts.

2.0 PUBLIC AWARENESS AND EDUCATION

2.1 (a) In our experience there is widespread and growing interest in genetics among the public, specifically in issues regarding human genetics. When addressing meetings of Quakers we have encountered a whole range of responses but have found that on the whole the young Quakers are more articulate than older generations in expressing the undesirability of manipulation of human traits and of marginalising genetic difference.

We consider that knowledge among the public is generally still extremely limited as polls have indicated, e.g. the 1993 EU-wide survey on Biotechnology and Genetic Engineering.

(b) Educating genetics is highly desirable, but should always contain the ethical dimension. There should be public representation on all ethical committees and the public should have full and unrestricted access to public registers of licences being applied for and experiments in progress.

There are still too few scientists communicating in understandable ways what they are doing and the possible implications of their research. Transparency and participation are some of the hallmarks of a just and healthy society.

As a matter or urgency the public should be encouraged to participate directly in as many ways as possible e.g., as demonstrated recently by Professor John Durrant (Science Museum) at the first UK National Consensus Conference on Plant Biotechnology. The Councils of Churches in Britain could also be asked to inform themselves and express their views.

2.2 Anxiety and suspicion are justified because the drive to "create wealth" is seen all too often to override other considerations. Wealth for whom at who else's expense? Evidence to a recent House of Lords Science and Technology Committee on "UK Regulation of Biotechnology and Global Competitiveness" contained references to the great value of the 'cancer market' and 'the AIDS market'. There was repeated emphasis on the huge profits anticipated by the bio-industry and on the necessity for as little regulation as possible to maintain our competitiveness, especially with America and Japan. The Lords accepted this. Genetics is being subject to increasing worldwide competitiveness and ethical concerns are likely to be overridden. The public does notice that large-scale supposedly "safe" technologies can lead to large scale catastrophes, e.g. Chernobyl, and Bhopal.

The military use of genetically engineered organisms is also possible as the need for a Biological Weapons Convention shows. Reassurance can be in many ways e.g., by setting up the proposed UN Human Genetics Agency (see 1.6, particularly section C 4 and 5).

2.3 We cannot judge whether expectations are unreasonable until we have seen the outcome. Expectations are however, extraordinary high for a technology still in its infancy. Patrick Dixon has commented: "the gene revolution is the most powerful scientific revolution in the history of human discovery, with the power to change every aspect of our lives, and even to change irreversibly the nature of human life itself" (The Genetic Revolution, Kingsway Publications 1993).

Scientists and those involved in promoting genetically engineered products and technologies should not falsely feed high expectations.

2.4 Yes: the old dispute about the relative importance of "nature or nurture" will continue but instead of "nature" the term "genetic predisposition, or "genetic" will be used to explain anti-social behaviour. We already hear rumours that geneticists expect to find genes that will cause alcoholism or deviant behaviour. It is a very dangerous trend and should not be used to justify reductions in social programmes of health, education and welfare. Attributing human personality largely to genetics is a negation of Christian belief.

2.5 Questions to be considered include:

(1) How could genetic changes be correlated with the complex behaviour of the whole person?

(2) How could genetic changes affect the human brain in its search for self knowledge and understanding of external reality?

(3) A practical ethical test that can be applied is to ask oneself the question—would I agree to a particular genetic change being engineered on myself, my wife or son, daughter, mother or father?

(4) How would particular genetic changes affect the gifts, dignity or beliefs of the individual concerned?

(5) Why make any genetic changes if they are not needed using the medical test of non-maleficence?

(6) Our current attitudes, beliefs and thought processes are the end result of evolution so far—won't the widely held idea that we are part of God's creation be destroyed when we have learned to manipulate our own genes?

3.0 Genetic disease

3.1 We do not have sufficient knowledge to comment.

3.2 No comment.

3.3 (a) Information about a person's genome must be regarded and treated as confidential. Insurance companies should continue to manage with questions about causes and age of death of parents and siblings, as screening could deny a person's right and access to equal and fair employment or to health and life assurance.

At present there are no rules governing the use of the results of genetic testing by insurers. Already however women are pressurised by invisible social and financial forces into choosing to have foetuses with genetic "defects" aborted. ("Defects" we feel is often an inaccurate term to describe these conditions and we apologise for any offence we might cause by using this term. hence the inverted commas).

This area should be an urgent and major priority for the government to clarify and regulate. It must not to be left to the insurance industry to choose voluntarily how to regulate themselves. We fear too that results of such screening could reduce government financial support for disable people. The Clinical Genetics Society which brings together medical geneticists in the UK, is now demanding that a statutory body be set up to control the use of gene tests for inherited diseases. (The Splice of Life, *ibid*, October 1994),

(b) Current medical tests can be positive whereas the outcome of analysing the human genome remains largely speculative. People can be unfairly victimised if the knowledge were made public. There is still a worryingly high possible margin of error in such tests.

3.4 The screening of whole populations cannot be justified as it would generally discriminate unfairly against the individual. Only in an unlikely extreme case of great danger to the whole population would screening be justified; It is not public policy to screen for HIV infection because only a small percentage of the population is likely to become infected.

If population screening were to become necessary then it should be a matter for national government to decide, and to make the necessary large resources available, including for large scale counselling and treatment.

The screening would need to be registered on a national data base to ensure completeness, but confidentiality would be hard to maintain, leaving individuals exposed to discrimination.

3.5 People should be protected from discrimination as a result of genetic screening tests. However it is very difficult to see how it could be prevented because of the disclosure requirements for life and health insurance. Discrimination could be legislated against but this would only be partially successful.

3.6 In cases where there are known familial defects voluntary screening could be justified. Where a sex linked disease gene is concerned screening might be postponed until the sex of an unborn child was determined.

Whether sexual partners are likely to want screening or not will depend on many factors including their religious ethics, their maturity, and level of education. Further research will not affect these personal considerations.

4.0 Eonomic benefits

4.1 In principle, once the gene code has been found it may be possible to interfere directly with gene reading function or suppress synthesis of the protein coded for.

4.2 Yes there are differences in principle. The effect of manipulating the human genetic make-up remains highly speculative and uncertain; this is much less so with conventional therapy. An illustration of this uncertainty is revealed in a recent edition of the journal Science: scientists have now discovered that the 97 per cent of the DNA code previously neglected as "junk" carries a significant message (*The Guardian* 8 December 1994). "We know what we know; we don't know what we don't know, until we find out more".

When considering development costs it is essential to consider the alternative ways such resources could be utilised. We already know that the suffering of millions of people could be reduced by the expenditure of relatively small amounts of money e.g., on oral rehydration and vaccination programmes for children in economically deprived countries. We must not let this technology widen the gulf between rich and poor people.

4.3 The possibility of claiming patent protection undoubtedly exerts a very strong influence on the commercial exploitation of research findings. The ownership of patents gives added power to those who own them and cannot be viewed as "morally neutral" as some would claim. The US, supported by Japan and the EU insisted that patent protection be included in the GATT negotiations and deals. This somewhat back door way

of forcing patents onto less industrialised countries who lack, as yet, the infrastructure to evaluate them and the resources to enforce them, cannot be regarded as morally neutral or of no commercial interest.

The overwhelming majority of less developed countries still have no genetic engineering regulations.

The promise of huge commercial gains that patents may offer could well tempt companies into bringing techniques or products onto the market without sufficient regard for potential hazardous effects. As David Suzuki and Peter Knudtson have commented: "the application of scientific knowledge is determined to a large extent by the turbulent, often value-free forces of the market place and an overriding economic imperative to profit quickly from new discoveries". (Genethics, Unwin Paperbacks, 1990).

4.4 We welcome the publishing of the UK regulations concerning the release of genetically modified organisms into the environment. There should be similar regulations in other European countries to ensure compliance with the European Directive.

However, the overall control of the situation implied is somewhat illusory as there is often insufficient scientific knowledge to answer many of the regulatory practical questions with meaningful precision.

Also the European Directive is currently being weakened by revisions aimed at maintaining European commercial power in the increasingly competitive world market.

5.0 Research

5.1 Mapping and sequencing are two different but related activities. Mapping involves finding landmarks at fairly frequent intervals along the genome. Such a map would speed up the process of working from family studies of a particular genetic trait to find the precise stretch of DNA associated with that trait.

Sequencing is the more exhaustive and labour intensive process of determining the exact nucleotide sequence of a stretch of DNA, or in this case of all the human genome. This gives the baseline information about the composition of genes and surrounding genomic regions (relatively little of the genome is believed to consist of genes as such).

Sequencing a gene is an essential step in its study. We would emphasise again that having the sequence of (some representative examples of) the human genome gives baseline information only in the sense that an A-Z of London does. It does not answer the questions that people want to ask: questions about what defines a person (or an organism), what gives them identity, how they develop normally and abnormally, how they are related to other individuals and other species, and how they age and die?

5.2 Piecemeal studies are directed at conditions and genes that are particularly interesting to some scientists. This may introduce a bias because society is particularly interested in quite specific areas of biology, such as disease and other "abnormal" states of the organism and human behaviour including topics like intelligence and sexuality. As members of society some scientists may therefore be more inclined to focus on these. These topics are often the ones to attract public support and funding.

This could mean that potentially significant areas, not currently in vogue will not be investigated e.g., as noted earlier recent work indicates the so called "junk" DNA carries some kind of significant code.

5.3 Most scientists, we believe, would argue that there is a continuum of influence between genetic determination and cultural/environmental conditioning ranging from virtually 100 per cent to very little, either way depending on the characteristic being considered. The characteristics that most people are really interested in, are the ones concerning disease and human behaviours. The answers to questions about the relative influences of genome and environment on these traits will have direct implications for developments in many areas including philosophy: the nature and meaning of individual personhood; spirituality; systems of religious belief; psychology and the sense of self; the meaning and understanding of consciousness, and also in practical areas such as social policy etc.

> *"The vulgar error that confuses heritability and fixity has been, over the years, the most powerful single weapon that biological ideologues have had in legitimating a society of inequality". (R C Lewontin, The Doctrine of DNA, Penguin, 1991).*

5.4 (a) A reasonable amount is known about the way genes are arranged on the chromosome, what sequences are important in the control of gene expression, and what sorts of defects will adversely affect it. This knowledge has permitted the manipulation of genes and gene expression in vitro and sometimes in vivo. Relatively little is known about the significance of various types of genetic organisation, about how various genes are switched on and off at the right times in development and how the level of gene expression is regulated under various conditions. Although gene expression can be controlled in artificial conditions in the laboratory (in vitro) this is very far from being able to replace the normal level of expression of region-specific and stage-specific aspects of a particular gene (in vivo).'

(b) Gene therapy might have unforeseen effects because it is still not possible to insert a foreign gene into a human or other genome at precisely the right place and in only that place. If a piece accidentally inserts into another gene and disrupts its function, the consequences could be severe, particularly if controls on normal cell growth were affected (a tumour might result). At our present level of understanding the effects of genetic manipulations, particularly in humans (because much prior experimental work is done on other species) are largely unpredictable and we must expect that to remain true unless or until a considerable body of experience is accumulated.'

6.0 Evolution

6.1 It is believed by many anthropologists that the various branches of the human race had a common origin in Africa some two or three millions years ago. Since that time physical differences encoded in the genes have become clearly visible. It is difficult to imagine a rational argument in favour of this slow process of evolutionary change having stopped: why should it? The physical agents (e.g., ionising radiation and cosmic rays) and chemical mutagens are still present in the environment as they always have been.'

Biological evolution, which cannot be stopped now is complemented by cultural, mental, and perhaps spiritual development, a new kind of evolution? There are many instances of collective development of species in such qualities as compassion, self-realisation and empathy.

6.2 The consequences of modern social organisation for human evolution are almost completely unpredictable. What must be regarded as astonishing is that evolution has reached the point whereby the process has become reflective, i.e., we are now conscious that it is going on. This gives evolution a new twist. The human "know-how" that is *replicated by cultural transmission* rather than by sexual reproduction has become a conspicuous feature of the environment. (Babies don't collect it with their genes but the National Curriculum will get them in the end!). Because humans can change their environment so readily to suit themselves and on such a scale, they have become unlike other organisms that are simply subject to environmental pressure; humans are now active agents of new and often extreme pressures on the environment. These may be technical as in the case of Chernobyl, or a combination of medical and religious factors e.g., premature babies, possibly carriers of a new mutation are now often saved because of personal and/or religious beliefs in the sacredness of individual lives.

6.3 Scientific knowledge is directly involved in two opposite ways with environmental change and its implications for evolution. First, it underpins the technologies that by their scale threaten the capacity of the natural world to respond (e.g., to burning fossil fuel) except by one or many species dying out. Second, only scientific know-how coupled with wise policies can prevent this destruction.

Environmental effects on evolution are so complex that predictions are of limited value. At the least there will be some changes when the temperature or radiation levels change, externally or internally, or from eating contaminated food, or from weakening the ozone layer leading to raised levels of mutagenic ultra violet radiation, e.g., it has been reported to be the cause of increasing blindness in sheep in the southern part of South America, and there is no reason why humans should not be affected also. This would constitute a powerful selective pressure on many people in less scientifically based cultures.

6.4 So how might biotechnology affect the human future? It is tempting to toy with notions of shaping the course of human evolution. But it is one thing to make good the consequences of a disabling genetic inheritance and another to improve on what we find ourselves to be. To what fundamental problem would any attempts at human stock-breeding represent a possible answer? Whatever grounds we may have for dissatisfaction with the human condition they will not be resolved by a technical fix because we are never likely to predict the way our evolution will turn out (except perhaps in ultimate disaster). Manipulation of the germ line in the laboratory would involve selecting characteristics to match a "model" human against some model of the environment that could not be other than limited and at worst dangerously misleading. What we do know about "Nature" is the extent of our ignorance.

6.5 The evolutionary impact of selective fertilisation or termination or other forms of discrimination depends on the motives, and wisdom or bias of those who control developments in genetic engineering or their application. Military dictators might prefer to have ranks of male babies to supply future armies, or various forms of eugenics might be practised, e.g., "ethnic cleansing".

On the positive side a policy of termination to avoid genetically determined illness according to agreed ethical guidelines could be justified.

6.6 The deliberate and controlled nature of such intervention breaks new ethical ground and any error made could be perpetuated for ever.

In the hands of greedy, unwise, ignorant or evil people this technology could be abused. We all know too well how the eugenics programme in Germany led to the appalling treatment of various minorities in addition

to the Jews. In the USA earlier this century there was a movement to sterilise compulsorily those classified as "feeble minded". In India there has been compulsory sterilisation of women with learning difficulties. (*Genethics News,* May/June 1994).

None of this could have occurred naturally.

6.7 Clinical intervention in sexual reproduction may suggest the end of love relationships as new technologies make it possible to sever links between sexual intercourse and pregnancy. This could have deleterious effects on future generations. We recognise that some new technologies could be beneficial and might offer people their only chance of having a biologically related child or reduce the risk of giving birth to a child with severe disabilities or genetic disease. We feel however that new reproductive technologies should not be further developed without clear societal directions grounded in collective, ethical and other values and priorities. Nor must women be inadvertently, or through lack of information, be exposed to risk and insufficient control over procedures and practices.

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We gratefully acknowledge many valuable suggestions and contributions from the following Friends: Joanne Bower, Barbara Potter, Jackie Leach Scully, Ioan Thomas

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Memorandum from Professor Nick Hastie, MRC Human Genetics Unit, Edinburgh (HGC81)

GENERAL ETHICAL AND REGULATORY ISSUES

1.1 It is impossible to say at this stage what level of knowledge is required to avoid all pitfalls. In the long run all the questions will be answered, but at present the timescale is not known. Key issues at this stage include:

(1) how proteins function and interact with other molecules; and

(2) the consequences of misregulation i.e., expression at abnormal levels and in inappropriate places.

With respect to the use or regulation of genetic information, it must be stressed that there cannot be a single set of guidelines; guidelines must be appropriate to the use to which the genetic information will be put.

1.2 This is an area where all research funding bodies must be vigilant. The policies being pursued by the MRC with regard to ethical and social consequences should be adequate e.g., the MRC requires all applicants for funding, and its own staff to seek full ethical approval when required (the MRC reserves the right to refuse funding on ethical grounds even where approval from an ethical committee has been obtained); the MRC has relevant representatives of e.g., health depts on its various committees and boards. I am less aware of the policies of other funding bodies.

1.3 Yes. However, as long as there are regulatory bodies constituted of appropriate people then this should not become a major problem (of course there will always be those which disagree with the recommendations of the regulatory bodies).

Geneticists surely do think about the wider moral issues and it is highly unlikely that there are "hidden agendas". However their role is to take forward science "to the benefit of mankind", and as long the providers of their funding take heed of the recommendations of the regulatory bodies (which will represent society's views) then there should be no risks.

1.4 To some extent the public may well take a deterministic view of human behaviour, however this is an issue which is not straightforward; it is not necessarily the research which is leading to this view, but rather the way it is presented. A better "public understanding" of genetics is important in this context.

It is possible that some people would wish to "improve" the world, although what is good in one person's opinion is not always good in another's—proper legislation would prevent abuse.

1.5 Currently it is not possible to manipulate the germ line. *At this stage,* no social or scientific situations can be envisaged where germ line interventions could be justified; there should be legislation to this effect.

1.6 I do not know much about this, presumably steps will be taken to ensure that the body preparing the declaration will have all the relevant scientific information as well as information on moral, religious, social issues.

PUBLIC AWARENESS AND EDUCATION

2.1 There is bound to be a variation in knowledge and interest across the various sectors of society. Clearly the interest is there but the level of knowledge is too low. It is vitally important to improve public awareness of the basic principles of genetics e.g., through the national curriculum, science festivals, media, and open days in scientific institutions etc.

2.2 There are bound to have been surveys which show that there is some anxiety and suspicion about research in genetics. Currently this anxiety is unjustified to my mind, but we must make sure that this is always the case. Therefore, the main issue is to concentrate on improving public awareness so that people can make their own informed judgments.

2.3 The answer to the first part of this question is "yes", the public already think that scientists can do more than they can in reality, however, the media, commercial interest and indeed some scientists are not blameless in this respect.

Unreasonable expectations should be tempered as they can be damaging particularly to those who suffer (or whose families suffer) from genetic disease. Improving public awareness must again provide the answer.

2.4 There is a danger that genetics will be seen as an excuse for socially unacceptable behaviour but environmental factors play a major part and this needs to be understood by policy makers (and the public) to ensure that genetics is not used as an excuse for unacceptable behaviour, or as an excuse to cut health, and education programmes.

2.5 I do not feel qualified to address this issue.

GENETIC DISEASE

3.1 There is not very much routine "service" genetic screening (Nairne report) therefore most screening is "research"—development of diagnostic tests etc. There are links between researchers and the routine medical service but there are problems, for example, there is a lag between research and routine screening (including the problems of defining when research becomes routine, and identifying who will pay); this is now a rapidly increasing problem as more and more diagnostic tests are being developed.

Whether or not a diagnostic test should be developed must be influenced by the availability of treatment/prevention programmes.

3.2 No.

3.3 The rights of the individual must be considered and protected as far as possible, but "how far" is not something which is easy to answer, there will need to be guidelines/legislation. The interest of employers should only be in the context of wanting to know whether the (potential) employee has a known condition which may affect their ability to do the job (or their own safety or that of others); most employers already ask a question to this effect. There should be legislation to state that genome information is private. Employers should provide regular health checks.

3.4 There is a range of factors which should be taken into account before deciding to undertake population screening for a genetic disease, e.g., prevalence whether it is a congenital disease, whether their is a known "at risk" population, the burden on society, the cost, the availability of treatment/prevention programmes etc. The resources for proper genetic counselling should be increased, and there should be a central body which reviews existing and proposed screening programmes.

3.5 There should be legislation to help to protect against any type of discrimination.

3.6 This is really a matter for the individual. It is not possible to generalise, but it is likely that perceptions will gradually change.

ECONOMIC BENEFITS

4.1 This is an important issue as our expectation is that the knowledge of disease gene structure will form the basis of rational drug design in the future.

4.2 There are no differences in principle between gene therapy and conventional therapy, but there are differences in practice. Gene therapy is at its embryonic stage and therefore, like any new therapy, it will be expensive. Once more is known about this type of treatment the costs will come down, and as it will be a rational, targeted form of treatment with minimal (one hopes) side effects it could become less costly to "trial".

4.3 I am not qualified to answer this question in detail; however it is clear that these issues will greatly affect the commercial exploitation of research findings, as indeed they affect the commercial exploitation of all (relevant) scientific findings. Patent protection is required for example to keep down the costs. However, we must guard against patents being applied to inappropriate targets e.g., gene sequences. There needs to be a better understanding of these issues; perhaps the most effective way to tackle this is to provide more experts who can advise the scientists.

4.4 I am not an expert in this matter, but regulations will influence investment, and it is the case in the UK that there are problems with raising venture capital (there needs to be an early exit route). It is also clear that in the UK we do not have that many people with the right blend of skills in this area.

4.5 There is a range of "products" which will be produced as result of human genetic research e.g., improved strains of farm animals (and possibly plants), new computer technologies, information systems, and databases.

Research

5.1 It is necessary to map the whole genome to position the genes. This is essential to:

(1) In the first instance identify all the genes associated with genetic disease.

(2) Help to understand how humans develop and function; and,

(3) To help to understand human evolution. I am not convinced that in the short term at least there is a need to sequence the whole genome.

There are two advantages to mapping and sequencing expressed genes:

(1) It is the genes that encode the proteins which are the functional units of the body and it is the genes which are usually mutated in human disease.

(2) It will be much simpler and cost-effective to map and sequence the genes themselves.

However, ultimately to understand genomic organisation, evolution, and long-range control of gene expression it will be essential to sequence the non-gene containing parts—perhaps focusing on specific model regions.

5.2 It is necessary in order to get the whole picture of human genome organisation, chromosome organisation, evolution, and genetic interaction. The complete picture will not emerge from piecemeal studies, or will surely come much more slowly and with more redundancy and expense.

5.3 Human characteristics are influenced by both genes and the environment. However this is a complex issue, for example characteristics are affected to different extents by the two influences, also the reverse is true, i.e., human characteristics can influence the effect of genes and the environment. It is also important to recognise that the internal environment can be a relevant influence.

5.4 There is quite a lot known about the organisation of coding information over a "short range" in the chromosome, however less is known over the "long range"; we are beginning to identify the important elements and the questions. It is conceivable that gene therapy will have effects that are unforeseen at this stage, however the issues will become clearer as knowledge increases and proper systems of control/regulation will be put in place (there is, of course already legislation governing gene therapy).

5.5 Financial support for basic human genetics research (e.g., sequencing and mapping genes) is probably adequate (in the context of the availability of research funding overall). However, there is insufficient funding available for biological research (which is necessary to understand the function of the disease gene).

Evolution

I must preface this section by saying that it is not possible to view evolution as a single, global entity as the ability of man to influence evolution varies throughout the world for example the First World has more influence than the Third World. Also the issue of timescale i.e., micro-evolutionary change or macro-evolutionary change makes discussion of this rather simplistic.

6.1 In Western society the effect of selective forces has been reduced, but not completely eradicated. Most people are now living beyond child-bearing age. However dramatic changes in the environment, e.g., increased pollution could select against asthmatics (many of whom have a genetic predisposition). New and unforeseen bacterial or viral epidemics could take their toll and exert selection for or against individuals with particular MHC haplotypes for example. This is more likely to happen in the third world. Genetic intervention is bringing about very minor evolutionary changes by, for example, selecting against certain dominant and deleterious conditions. On the other hand, we are now selecting for certain deleterious genes which would previously have been lost under more stringent conditions e.g., myopia.

6.2 In the Western world in particular with more mobility and a more densely packed population there is more intermixing—if anything leading to a healthier population. This will also result in less genetic drift and less chance of evolutionary selection.

6.3 This must vary throughout the World depending on how much man can influence or overcome/avoid the effect of the environment. However the effects could be enormous in some parts of the world. See above for more description.

6.4 Where the pursuit of scientific knowledge leads to improvements in health and/or the environment there may be minor effects on evolutionary change. However this is a complex issue, e.g., some changes may, in the long run, be beneficial whereas others may be detrimental. This is another area where proper legislation is essential.

6.5 The possible effects of selective fertilisation or termination on evolution are hard to judge—but are most likely to be small. If a trait is recessive then "treating" it would not affect the gene pool, however if the trait was dominant then "treating" it could eradicate the gene. With respect to rare diseases the impact on evolution of eradicating them will not be great. With common, multifactorial conditions selective termination or fertilisation (unlikely events) will have very little, if any, effect on evolution.

6.6 Manipulation of the germ line in the clinic/laboratory varies enormously from natural variation as it could create forms which would not occur naturally.

6.7 The term "clinical intervention" is such a catch all term that the question is unclear.

Memorandum from Mary Kearns, Solicitor (HGC82)

1. General ethical and regulatory

1.2 The following types of research project require careful and rigorous regulation—

(a) Those projects involving research on live human subjects;

(b) Those projects whose goal or likely and foreseeable applications would have profound ethical or social consequences. Research falling into either of these categories requires regulation against a proper moral and ethical framework (see 1.5 and 1.6 below). The Declaration of Helsinki contains valid recommendations and guidance on research involving human subjects which are appropriate and applicable here. It provides (at Article I.5) that "concern for the interests of the subject must always prevail over the interest of science and society". Thus, the Declaration recognises that the interests of an individual human research subject are distinct from those of (a) the scientist and (b) society as a whole. To the extent that existing controls do not recognise this three-way conflict of interest, they are inadequate. (See 1.6 below).

1.3 (i) Society must have the right to regulate research falling into either of the categories in A and B above. It is unlikely to be the research *topics* themselves which should be prohibited but rather *methods* which might be used to conduct research (e.g., germline intervention in the genome of an individual for non-therapeutic purposes or where the risk of harm was unacceptably high). Alternatively, it might be the intended or foreseeable application of techniques developed as a result of the research which should be prohibited. In either event, society must have the right of regulation.

(ii) Geneticists in common with all professionals always have a duty to act responsibly. That duty is owed to society as a whole as well as to individuals directly or indirectly affected by their research. Where they are involved in projects with social or moral implications they should consider these carefully against a proper moral framework. However, there would be a distinction in their approach as between two categories. With regard to projects in category A, geneticists are and should be responsible for research methods used on individual human subjects. Regulators should also be responsible for ensuring that these methods are strictly in line with the moral framework.

With regard to category B, geneticists bear less direct responsibility for the consequences and applications of the research results. Whilst scientists bear moral responsibility to the extent that these consequences or applications are foreseeable, Regulators should have legal responsibility for the ultimate application of the techniques derived from the research.

Thus, certain types of research require to be regulated by both scientists *and* independent Regulators because of their moral (and possible constitutional) significance.

(iii) If scientists (and Regulators) fail to follow a proper moral framework (see 1.6 below) they will be suspected of pursuing hidden agendas.

1.4 (i) The word determinism has been used by different people to mean different things. The OED. defines

determinism as "the theory that action is determined by motives, themselves determined by causes independent of the will. In this sense, it seems likely that research into human genetics would lead to a deterministic view of human behaviour (e.g.,) that people are gay or prone to criminal behaviour because of their individual genetic make-up). The difficulty with this view of human behaviour is that it may ignore free will, intelligence, reason and environmental factors and assumes that people will always act in accordance with genetic pre-disposition. As a view of human behaviour it is flawed and could lead to extreme forms of discrimination.

(ii) People will undoubtedly try to "improve" the world through genetic interventions if the techniques for doing so are available. The difficulty is that improvement is a subjective concept. To use an extreme example, Hitler thought that he was improving the world by eliminating non-aryans.

(iii) If improvement is defined for this purpose as the combatting or curing of organic disease without challenge to the physical or psychological integrity of the subject then people should strive to improve the world *but* their efforts should always be subject to the moral framework and to very strict controls.

1.5 (i) Experiments on human subjects which involve germline intervention would only be morally legitimate if *all* of the following conditions could be and are met:

(a) The germline intervention is intended for therapeutic purposes (i.e., combating or curing disease) rather than destructive or purely experimental purposes. Furthermore, the intervention is intended for the therapeutic benefit of the individual subject (rather than society as a whole or any particular class of people).

(b) The intervention is likely to achieve its therapeutic aims for the individual subject.

(c) The intervention does not expose the life or integrity of the human subject (or his or her descendants) to disproportionate risks.

(d) The scientists and doctors concerned and the regulatory bodies are satisfied that the risks and likely effects of germline intervention are known; (if such knowledge is only limited as the question suggests, then that in itself would be an objection in principle to the use of germline intervention at this stage).

(e) Proper informed consent has been given by the subject or his or her parent or guardian where the subject is a child (born or unborn) or an embryo. In the life of the human subject, the earlier the intervention takes place, the more difficult will be issues of consent. The duty in relation to germline intervention to carry it only for therapeutic and not for destructive or purely experimental purposes is a duty owed to a human subject from the moment of conception. If it became possible to perform germline intervention at the embryonic stage, the embryo should be accorded the status, dignity and rights of any other human being. (The writer does not accept the highly artificial concept of a "pre-embryo")

(f) The recommendations set out in the Declaration of Helsinki have, in all other respects been observed.

1.6 The life of the subject and the integrity of the genome must be protected at all times. Subject to this overriding concern, germline intervention might be permitted in order to cure a serious disease in the individual human subject. The Helsinki Declaration should be used as the basis of any UN Declaration and treaty. The basic principles contained in that Declaration are as applicable to treatment as they are to research. I would add to Article I.5 of the Declaration a recommendation that states should set up bodies to safeguard the rights of the research subject. It should be appreciated that the rights of the individual research subject are or may be in conflict wiht the interest of society as a whole. It would not, therefore, be acceptable for states simply to set up Regulators comprised of "a cross section of society" as has been the case with other regulatory bodies in the past. Instead, membership of such bodies should be restricted to those most likely to safeguard the human rights of the individual e.g., representatives of patients' associations, church men or women, GP's. and other medical specialists not involved in the research, lawyers and representatives of civil liberties associations.

Furthermore, the individual human genome should be protected from the time of conception and the recommendations of the Helsinki Declaration as amplified applied from that time. Destructive or purely experimental research on the human genome should not be countenanced at any age or stage or gestation.

Any Declaration or Treaty in relation to the protection of the human genome should be ratified by Parliament and given proper effect. I would submit that it would be necessary to have not one but two Regulators because of the inherent conflict of interest. One of the Regulators would be charged with responsibility for the moral and social consequences of research or treatment and with ensuring that the provisions of both the Declaration of Helsinki and any UN Treaty or Declaration in relation to the human genome are met; the other Regulator would be charged with looking after the interests of the individual research subject or patient.

2. PUBLIC AWARENESS AND EDUCATION

2.1 Steps should be taken to improve knowledge of and interest in genetics among different sectors of the public. Regulators should be required to produce public reports. The public should be made aware of the moral

framework against which the research is being conducted. Whilst scientists can indicate the benefits of research into the human genome, it is not only a question of benefits but of important human rights. Care should be taken that the human rights questions receive sufficient attention. This could be done by reports, consultation and public debate.

2.2 Yes, there is a general anxiety and suspicion about research into genetics. It can be allayed by proper respect and legal protection for the human genome.

2.3 I am unable to say whether the expectations are unreasonable!

2.4 There must be a danger that genetics could be seen as an excuse for socially unacceptable behaviour. If an entirely deterministic view is taken of human behaviour, genetics could be used to justify reductions in social programmes of health, education and welfare. The justification put forward would probably be that there is no point in spending money in some of these areas because the genetic profiling of the individuals concerned suggests that the money is not being spent efficiently and that it would not make any difference to the outcome. Whilst there may be some merit in arguing that funding should be "targeted" appropriately (e.g., that screening for breast cancer should be given to all those with a genetic pre-disposition). It is easy to see that such targeting might get out of hand under pressure from the Treasury. Whilst it might be acceptable in some instances to target certain types of preventive health care on those with genetic predispositions the genetic targeting should not be to the exclusion of other "at risk" groups. It would be unacceptable if genetics were used as an excuse for failing to meet need.

2.5 Genetics should be seen within an ethical framework rather than the other way round. All human beings should have status, dignity and rights under the law. If this is used as a starting point, the questions are obvious. If genetic factors are used without regard to all other factors then society's view of human behaviour, personal responsibility and ultimately ethics will become distorted. This is why care should be taken to present the matter in a properly balanced way.

3. Genetic disease

3.3 Information about an individual's genome should be regarded as confidential. Most employers could have no legitimate interest in requiring genetic tests. It is not difficult to see that genetic testing might well distort the insurance market. Clearly, if there were a way for insurers to eliminate or minimise risk by refusing cover to people with certain genotypes then commercial considerations are likely to produce that result. Thus, people with certain genetic profiles would be either unable to obtain insurance would only be able to obtain it at great cost. The difference between genetic testing and current medical tests is one of degree rather then principle. It would not be in the interest of society (or ultimately, of the insurance market) for details of an individual's genome to be available or for insurers to be able to make it a requirement of cover. It could result in insurance companies refusing cover to the people who need it most. Equally, it could result in employers refusing employment to individuals for unacceptable reasons. Ultimately it would be likely to result in genotype discrimination which would be difficult to combat.

3.4 Population screening for genetic disease would only be appropriate where the health service was in a position to offer either prevention (of the disease rather than elimination of those carrying it) or cure. People should never be screened for any genetic disease without their informed consent. Counselling should be carried out at the stage of seeking informed consent rather than after the event. Because of its human rights implications and the possibility that screening could be used for discriminatory purposes, screening should be regulated closely by the Regulators suggested above.

3.5 This sort of screening should not become routine in the absence of proper counselling, consenting and the availability of prevention or treatment. If it were to become routine, it would be necessary to give people legal protection from discrimination on the grounds of their genotype. This would probably have to take the form of the current law in discrimination on grounds of race, sex or marital status. Discrimination against people on grounds of their genotype would be as unacceptable as any other type of discrimination against people based on characteristics over which they have no control.

3.6 Yes, people would be well advised to seek genetic information before the conception of children. However, this is unlikely to happen.

6.5 It is encouraging to note that the Committee recognises that selective termination is a form of extreme discrimination.

In conclusion, I would submit that it is imperative that any research or treatment which involves interference with the human genome or intervention in the germline is conducted against a proper moral framework. During the House of Commons Debate on the 1990 Human Fertilisation and Embryology Bill the following argument was put forward by Bernard Braine:

"When one bases decision making on the proposed benefits of a type of research rather than its morality, one will always be under pressure to extend that limit when greater benefits are envisaged. That is no way to make law. The anticipated benefits seem compelling but they are misleading (House of Commons, *Official Report*, 2 April 1990 col. *934*)".

The writer is a lawyer specialising in civil litigation with a special interest in medical jurisprudence. The writer has studied medical jurisprudence and human rights at university and is a past recipient of the University of Edinburgh Berriedale Keith essay prize in Human Rights.

Memorandum from Professor Steve Brown Department of Biochemistry and Molecular Genetics, St Mary's Hospital Medical School (HGC83) (30 December 1994)

I apologise for my late response to the House of Common's Science and Technology Committee inquiry into ethical, regulatory and economic implications of human genetics research. I understand that you are prepared to receive some late responses. Rather than framing my responses to individual questions, I have tried to give an overall response to the key, critical points raised in each section:

1. General ethical and regulatory

Anybody who has witnessed the growth and determination of many charitable organisations founded and supported by sufferers of various human genetic diseases will know that human genetics research is very much patient led—the satisfaction for scientists, aside from the intrinsic knowledge of knowing better how the human body works, is to watch the progress in medical research leading towards better treatment for a wide variety of serious disease that is genetically based. As with all medical research the answers may raise problems in areas of diagnosis and treatment—none of these are insuperable and usually revolve around issues of priority and need versus health care budget constraints etc. Nor do the present discoveries, diagnoses and treatments immediately raise fundamental moral problems.

Scientists will continue to explore the human body from all angles, including its genetics—we cannot hope to be able to set up a regulatory framework for genetic information without understanding it. Research in the UK, USA, France and many other countries with strong biological science programmes have made great strides in the understanding of the genetic bases for human disease. These advances are continually appraised in terms of the ethical and social consequences by the scientists themselves and by the funding agencies, including the MRC. But a more broader, reasoned public debate is required. The implications of the new genetics for our health and livelihood in the future cannot be ignored—there is nothing frightening here; but there is a vast potential to improve medicine and the quality of lives for many.

Although some would argue that the deterministic view of human behaviour or other human traits has been strengthened by recent advances in human genetics, this is an old see saw that could swing again. Undoubtly, the available technologies have allowed us to focus recently on the impact of genes, rather than environment, or behaviour and other human traits. As often happen, the appearance of a new technology—that of gene finding—has rapidly transformed the field of human genetics, perhaps one could argue distorted it somewhat, as scientists follow successful trends that will be responsible for a real revolution in medical understanding and treatment. Nevertheless, geneticists remain cognisant of the environmental components of human behaviour.

Leaving aside treatments, including somatic gene therapy, that are based upon a knowledge of the gene and its function, there has been continual discussion on the possibilities of germ line intervention for the correction of genetic defects—intervention that would inevitably be transmitted to future generations. The mechanics to do this successfully are not yet available but the question arises as to whether this is an area for which society may declare a moratorium on research given the rather difficult ethical problems that arise. I do not see this as an area where many, if any, scientists wish to be actively engaged. They see the hugh technical problems involved and the potential consequences of mistakes for future generations. Nevertheless, human geneticists are honest enough to admit that much genetic research that is presently carried out will have an indirect bearing on the technical feasibility of such and approach were it to be considered or sanctioned in the future. That is the nature of research—a vast interconnected web of discovery and invention—which may lead to future treatments, interventions, etc. It would be impossible to control research in an organised manner. What is required is when the consequences of research become apparent that the legislators then proactively introduce a reasoned, public debate followed by appropriate regulation.

2. Public awareness and education

(see also some comments above)

Inevitably, the general public know little—but members of the public involved with charitable organisations at the forefront of fighting human genetic disease are remarkably well informed. We need an education

programme on human genetics in all secondary schools. Human genetics will transform our health care in the next century and everyone will be touched by it. It is only through an active educational process that an informed and continuing debate on these issues can be held with the public. This will allow individuals to respond in this debate with reasonable and realistic expectations of what human genetics means and can do.

3. Genetic Disease

Genetic diagnosis is in its infancy in this country as in many other developed countries. In many cases, it is allied or piggy backs on research programmes. Given the costs and constraints on health care budgets, I do not see genetic screening programmes growing rapidly at present. The greatest demand at present comes for communities that are affected by a particular genetic disease—communities that have formed themselves into organisations that create a keen awareness of the possibilities of human genetics for screening and treatment.

The greatest problem remains the confidentiality of genetic information. Genetic information should remain strictly confidential unless permission is given to release it to employers, companies etc. In the UK, where we still have universal health care free of charge, and health insurance still has only a modest impact, access to health care will not be affected by one's willingness to part with "genetic profile" information to insurers. Nevertheless, insurance companies already require health screens for other types of insurance and employers often require some health check on assuming employment. It is difficult to argue that genetic information should not be asked for here. What is required is a different and more informed attitude on the part of insurers and other bodies as to the benefits and costs of taking into account genetic information. Genetic screening can reveal genetic variants that make an individual less susceptible to a disease compared to an average individual in the population. Genetic screening is just as likely to lead to the positive bill of health that we all hope for from an insurance exam at our GP—perhaps more so. Many will come away with the knowledge that we have good genes that we did not know about. We could expect to see reductions in insurance premiums and more people entering the insurance net. Nevertheless, for some we are faced with the possibility of the age-old insurance exam uncovering potential genetic susceptibilities to future disease, increased premiums and the consequent need for expert counselling. We have yet really to fully explore and answer these positive and negative aspects of our new found abilities to investigate our own health.

Our overall assessment of this developing and hazy picture should not be rushed—we are far away for screening programmes for many diseases. Few screening programmes, I believe, will ever be carried out on a community wide basis for reasons of cost. Many people will be uninterested to seek genetic information before conception—genetic education will make them realise that they cannot be 100 per cent protected—especially if only a limited battery of tests is available, as may be the case.

4. Economic benefits

Knowledge of the gene and gene product responsible for a genetic disease is the most powerful tool for developing treatments. This is why there are so many start-up companies, particularly in the USA, with a mandate to isolate genes involved with genetic disease. The economic implications are staggering. Since the treatments devised based upon the gene product are likely to be more therapeutic than conventional treatments, there is an argument to be made that costs may even be reduced.

Technology-transfer facilities and patent protection are vital for UK research to benefit from the excellent progress that has been made here. Many universities and research institutes are making vital discoveries in human genetics, discoveries that need to be developed and protected to ensure that funds flow back to the organisations primarily involved with the invention process. Sadly, venture capital in the UK has not exploited this area to the full. Most of the critical start-up companies involved with genomics and human genetic disease gene isolation are located in the USA.

5. Research

Sequencing and mapping the entire human genome leads to information about genome organisation and gene structure that is vital for fully understanding gene regulation and development of the human body. Given the immediate benefits that come from identifying the genes that underly genetic disease, mapping the expressed genes remains a priority, but there will be much to be gained from the knowledge of other sequences in the human genome e.g., the sequences that turn genes on and off at the appropriate time during development. Knowledge of overall genome organisation will have a vital role to play in better understanding how we and our genome evolve. It will also allow us to develop better ways of intervening and correcting genetic defects in our genome i.e., in developing better ways of delivering somatic gene therapy.

Overall, given the impact that human genetics will have on our lives over the next century, the investment into genomics in this country is woefully inadequate both from the point of view of public and private funding.

6. Evolution

As discussed above, the technology and mechanics of genetic intervention that could be passed to future generations i.e., germ line intervention, is not available. Nor does it appear likely in the foreseeable future. For this reason, I am sceptical that there is an issue to discuss with respect to the possible impact of human genetics on the long-term future of the human race. Even if germ line intervention becomes possible, it is fallacy to believe that it would be straightforward to alter the characteristics of a large species such as human. Indeed, this was a classic flaw of the eugeneic movement. We know that most human features and many human diseases are controlled by several, sometimes many, genes. Our make-up is governed overall by many complex combinations of genes inherited from our parents. Trying to alter these in any systematic way to alter the genetic make-up of a species is nigh impossible. Similar constraints apply to selective fertilisation or termination.

Memorandum from Professor Martin Bobrow, The Clinical Genetics Society (HGC84) and (HGC84A) (29 December 1994)

Answers to the Committee's questionnaire

The Clinical Genetics Society represents over 600 professionals engaged in the practice of clinical genetics. The membership includes medically qualified clinical geneticists, laboratory scientists interested in the various aspects of diagnostic laboratory genetics in health care, non-medically qualified genetic counsellors, and others with a professional interest in clinical genetics. The Clinical Genetics Society is well advanced in negotiations with its three sister organisations, the Clinical Molecular Genetics Society, the Association of Clinical Cytogeneticists, and the Genetic Nurses and Social Workers Association, to form a federated British Society of Medical Genetics. Even prior to the formation of this new body, the four organisations cooperate closely on policy issues. These are the only four bodies formally representative of the profession of clinical genetics in the United Kingdom.

As a responsible professional body, the Clinical Genetics Society has always concerned itself with the scientific and technical advances in its subject, the integrated delivery of services to patients, matters of health service organisation, and the social and ethical dimensions of the subject. Most recently, for example, the Clinical Genetics Society has considered and endorsed the Nuffield Council on Bioethics report *Genetic Screening: Ethical Issues.* The Society has also started work on drawing up detailed recommendations in such areas as the conduct of genetic registers, and criteria for screening trials for hereditary liability to diseases, that might be put to a central coordinating body, as recommended in the Nuffield report, should such a central body be created.

The CGS, together with other professional bodies of geneticists, has for some time been at pains to point out that there are social and some ethical decisions to be made in the clinical application of genetic technologies, which require a public debate. Decisions must be made by those more representative of society than the professional groups themselves. We therefore very much welcome the Science and Technology Committee's decision to hold this Inquiry. We look forward to a constructive dialogue which will serve to make the benefits of modern genetic knowledge available to the vast majority of the population who wish to make use of this information, while ensuring that there are clear and reasonable contracts between the professions and the public, as to the appropriate ways forward, at least in the near future.

Patenting and Clinical Genetics, A joint statement by The Clinical Genetics Society, The Clinical Molecular Genetics Society, The Association of Clinical Cytogeneticists, The Genetic Nurses and Social Workers Association

We recognise the importance of patent protection, in allowing the development of diagnostic and therapeutic products, for the benefit of health care. We distinguish a number of different situations:

1. *Novel techniques, apparatus or procedures for use in clinical genetics*

We view these as inventions in the conventional sense of the word, which ought to have the protection of patent law, subject to the normal restrictions on monopoly abuse.

2. *Patents on fragmentary sequences from human DNA, of no known function or utility*

We do not believe that such sequences should be patentable, partly because of the lack of demonstrable utility and partly because of the inevitable and unnecessary confusion which would arise when several groups were found to hold patents on parts of the same overall functioning sequence.

3. *Human gene sequences of known function and utility.*

(i) A natural gene sequence is not an invention, but is a discovered product of nature.

(ii) A natural human gene sequence is part of the human body, and as such should not be patentable. The suggestion that such a sequence might be patentable if it is "isolated in a pure form" or "isolated outside of the body" seems to us a sophistry, and should not be allowed.

(iii) There is only one consensus of normal human sequence. If the sequence as such is patentable, it will not be possible for anyone at any time to devise a better or different way of genetic diagnosis; this is inequitable.

(iv) Cloning a novel gene using one of the limited number of generally applicable cloning procedures requires skill and application, but not originality. If anybody has a claim to a patentable invention it is the originators of the procedures, not the laboratory which happened to come out ahead of the competition in applying the method.

For these reasons, the Societies are, in principle, against the granting of patents on human gene sequences.

The utilitarian argument against this stance, that lack of patent protection would discourage commercial enterprises from engaging in gene isolation, does not persuade us. First, any such discouragement is probably inevitable. There are a very large number of human genes which will be cloned over the next several years. On the test of novelty, patents may be granted on some of the first to be cloned but refused on others, just as useful or important, which are cloned later using the same methods. Allowing some patents will only produce arbitrariness and inequity. Second, most gene isolation to date has been done by public sector institutions, using government and charity funds, and greatly helped by the free inter-change of materials and information which has up to now been the norm in the non-commercial sector, but which is threatened by the rise of gene patenting.

Our opposition does not extend to the patenting of specific constructs containing human gene sequences which have particular utility. For example, a human gene sequence in a particular vector with a particular promoter might have utility for therapy; or an artificial construct might have specific value as a diagnostic reagent. These would be inventions, designed by human ingenuity, and in our view would be properly patentable if novel, non-obvious and useful. But we note that attempts at defensive patenting of natural gene sequences are already involving academic and commercial organisations in considerable work and expense, to the detriment of the wider interests of society. There is an urgent need to send a clear signal that such patents will not be allowed.

We wish to bring these views to the attention of the Government of the United Kingdom, and to the European Patent Office.

Martin Bobrow *President, CGS*

Andrew Read *Chairman, CMGS*

Margaret Fitchett *General Secretary, ACC*

Penelope Guilbert *Chairman, GNSWA*

INTRODUCTION

The Committee's questions are exceedingly wide ranging and complex. We have attempted to respond broadly, at the expense of detail in any one area. The following response is numbered to correspond to the questions received from the Select Committee. We particularly wish to draw attention to the following points:

(a) At least until further experience has been gained of the implementation of large scale genetic screening programmes in both NHS and commercial sectors, the Clinical Genetics Society supports the introduction of a central body to monitor and advise in this area of health care *(Question 3.4).*

(b) The availability of predictive genetic information to third parties, such as employers, insurers, and health care providers, could lead to socially discriminatory practices. There may be a need for careful monitoring, and possible legislative intervention, in this area *(Questions 2.4 and 3.3).*

(c) The Clinical Genetics Society remains opposed to the patenting of normal human gene sequences, and would welcome international legislation to clarify this very confused situation *(Question 4.3).*

(d) Further debate on ethical and social dimensions of human genetics will be assisted by much more pragmatic research, but there is a lack of trained researchers in this (and several other) fields *(Questions 1.2 and 5.5).*

(e) The Clinical Genetics Society welcomes programmes which improve public understanding of science, but does not subscribe to the view that better factual understanding will necessarily diminish the diversity of views on the pace, potential benefit, and hazards of applications of genetic knowledge. These important social issues demand wide social debate.

1.1 *What do we need to know about the way genes work in order to make decisions about the use or regulation of genetic information? Are we likely to obtain that information?*

The most important characteristic of genetic information, as compared to other diagnostic medical tests, is its ability to predict the liability to disease long before any clinical abnormality is present. More detailed information will clearly be required about the precision of prediction in each individual diagnostic or therapeutic situation. This information will be obtainable, but will accumulate gradually, because it is not generic, but is specific to each individual diagnostic or therapeutic situation. Since genes frequently operate in conjunction with particular environmental factors, further information on gene-environment interactions may allow the development of specific avoidance or therapeutic strategies for diseases with major genetic components. The nature, and speed of acquisition of such information remains speculative. Clinical implementation of genetic knowledge must, for the foreseeable future, be backed by continuing active programmes of research and evaluation.

1.2 *Are the current policies being pursued by the MRC and other research funding bodies with regard to ethical and social consequences of research in human genetics adequate?*

A number of national and international bodies have funded discussion and research on the ethical and social dimensions of human genetics. A voluminous literature has now been generated on this topic, much of it latterly becoming rather repetitive. There remains an important need for pragmatic research, based on study of patients and populations eligible for various genetic procedures, in order to put bounds on the extent to which *a priori* discussions and views (whether promulgated by geneticists, ethicists or protagonists of any other hue) have a generalised validity. **Such research is being funded by the MRC, the Wellcome, EEC and others, but there are an inadequate number of trained researchers in this field.**

1.3 *Has society a right to declare that some research topics should be prohibited because they are intrinsically likely to lead to insuperable moral problems? Should geneticists think more widely than their immediate research goals and their likely consequences, or should they leave that to others? Are they pursuing hidden agendas of which the public is unaware?*

Geneticists as a group have proactively drawn the long term potential consequences of their research to public attention. They *should* think more widely than their immediate research goals, and they have in general done so. They cannot leave that to others, because the special knowledge which geneticists bring to bear is important in keeping the debate rooted in reality, and because it is the geneticists who will themselves have to implement decisions which are taken. They should (and often do) work closely in conjunction with others. Geneticists are a diverse group of scientists, coming from many different social, personal and scientific backgrounds. It is almost inconceivable that any significant number of individuals could "pursue hidden agendas" in the face of this diversity.

Society would have a right to declare a research topic prohibited, at least partly because Society funds most research. However, such a decision should only be taken if the research leads inexorably to a severe moral problem which cannot be avoided by any other means than stopping the research, and if it is clear that the research is extremely unlikely to lead to any important benefits which would compensate for that hazard. It is extremely hard to imagine the circumstances in human genetics where anything resembling these criteria could be met.

1.4 *Does research into human genetics lead to a deterministic or any other particular view of human behaviour? Will people try to improve the world through genetic interventions? Should they?*

Genetic mechanisms act in concert with one another, and with very important environmental backgrounds. A major potential benefit of further understanding of genetics will be the further understanding of this environmental interaction, which is inherently more amenable to manipulation than are the genetic components of health and disease in themselves. Only when translated into the most simplistic headlines does a greater understanding of genetics lead to a deterministic view of human behaviour, or even of human physical structure and function.

1.5 *Germ line intervention would affect later generations who cannot give their assent. Are their other objections in principle to it which go beyond our limited knowledge of what those effects might be? Would this be playing God? What does that mean, and why would it be wrong?*

Mankind has always undertaken activities which affect later generations, without their assent. There is nothing novel in this principle. The extreme limitation of our knowledge of the effects of germline intervention is not, however, a trivial objection. Effects of germline therapy will certainly be long lasting, and difficulties to reverse. Until a great deal more information is available, which will axiomatically take a long time, such intervention should not be pursued.

2.1 *What is the extent of knowledge of and interest in genetics among different sectors of the public? Should steps be made to improve this and, if so, what form should they take?*

Recent studies have demonstrated considerable public interest in human genetics, and some concern at its potential applications. Adequate scientific knowledge assists in distinguishing likely from exaggerated claims (both positive and negative). For reasons much wider than those posed by this Inquiry, a better public understanding of the potential and limitations of scientific methodology for altering human society, in terms of

health and wealth, is required. Other societies, particularly that of the United States, appear to embrace science far more readily than does the United Kingdom. This has not lessened their ethical debate, and has consequences in other areas such as the willingness of the commercial sector to embrace new science and technology. It should not be assumed that a more informed public will be less critical of scientific innovation, but the debate may be at a more constructive level.

2.2 *Is there a general anxiety and suspicion about research in genetics? Is it justified or should it be allayed, and, if so, how?*

There is evidence that the public are somewhat more suspicious of research in genetics than are professionals; however, this is not an acute, but a relatively mild suspicion. The public also have high hopes and great appreciation of the potential role of genetics in alleviating human disease. Because of the novelty of recent genetic research, and the speed with which it is progressing, some suspicion seems entirely appropriate. There is no argument for artificially allaying such suspicion, but considerable reason to ensure that the scientific advances are well understood, and their applications are responsibly pursued, properly monitored, and controlled where necessary.

2.3 *Are there unreasonable expectations of the benefits that might come from genetics? If so, should these be tempered?*

The expectations of benefit from genetic research have sometimes been exaggerated, particularly in that the protracted timescale has not been adequately appreciated. It is too soon to assess whether the eventual benefit of genetic research has been exaggerated, or under-estimated.

2.4 *Is there a danger that genetics will be seen as an excuse for socially unacceptable behaviour? Could it be used to justify reductions in social programmes of health, education and welfare?*

We are not aware of any evidence that this has occurred in the United Kingdom. There have been concerns about potential social discrimination by others, on the basis of genetic findings. Possible use of genetic information by employers and life insurers, to exercise different forms of genetic discrimination, clearly merits further public discussion to achieve a balanced and fair solution. There is a particular concern, with continuing pressure on health budgets, that purchasers of health care will put undue pressure on those at risk of passing deleterious genes to their offspring. In China, according to press reports, a draconian eugenicist law has recently been promulgated, prohibiting those likely to have children with disabilities from reproducing. There is anecdotal evidence that health insurers in the United States have been reluctant to bear the costs of treating children with genetically determined disease born to couples who knew that they were at risk of such an event. The Clinical Genetics Society deprecates such practice. **It is important to eliminate abuses of this sort, by controlling the socially unreasonable and discriminatory practice, rather than attempting to restrict more responsible science or health application of genetics.**

2.5 *What are the right questions on the bearing of genetics on human behaviour, ethics and belief?*

This is a very complex question. It is important to remember that genetics only tells us *how* living organisms work; that they *do* work, we know already. We are well aware of the variations in human behaviour, and of our methods of dealing with these variations in society. That some of this variation may have an underlying contribution from genetic mechanisms should not necessarily alter our social and ethical framework.

3.1 *How much of genetic diagnosis is conducted as a routine medical service, and how much is associated with research programmes? Is the continuity between the two sufficiently well organised? Are some diseases with a known genetic cause not being diagnosed, and, if so, why not?*

We are not aware of specific, quantitative data on this question. All Regional Clinical Genetics Centres are now associated with DNA Diagnostic Laboratories. For those genetic diseases where diagnostic tests are well established, the great bulk of work is done in these NHS-supported laboratories. However, diagnostic tests have generally been developed in research groups, and in many cases research groups have continued to provide diagnostic services for some time—often for a considerable time—after the research questions had been answered. In some cases this was appropriate, while subsidiary R&D and health services evaluation continued; but in many cases it has represented difficulties in getting diagnostic programmes transferred from research laboratories to the NHS. It has, in general, not proven straightforward to get NHS purchasers to accept, adopt and pay in advance for service developments. It takes time to set up and train staff to run new services; and there is no easy mechanism for this development money being agreed in advance, and then reclaimed through service mechanisms.

There are particular problems in running diagnostic services for very rare diseases, where there are arguments for a limited number of national centres rather than Regional centres based on populations of one to three million people.

3.2 *Are there any ethical questions about somatic cell gene therapy which are different from other types of therapy which affect only the patient receiving them?*

The Clinical Genetics Society agrees with the views of others, e.g., the Clothier Committee, that somatic cell gene therapy does not raise any new ethical issues. Some established types of therapy e.g., cancer chemotherapy also carry a small probability of inadvertent damage to the germline, and of hazard to health workers delivering the therapy.

3.3 *Should information about an individual's genome be regarded as confidential, or should it be possible for employers, insurance companies etc. to require tests, or to obtain the results of previous tests on an individual or their relatives? If not, why is genetic testing any different from current medical tests?*

If third parties are entitled to access to genetic information, then those undergoing genetic screening will be placed at a social disadvantage. This may produce destructive conflict between their best strategy for maximising their future health (by undergoing genetic screening), and their desire to avoid such discrimination. Genetic testing differs from current medical tests in that it can predict disease far into the future, rather than revealing current disease. To allow insurance agencies, in particular, access to this information would produce a considerable shift in balance of advantage away from the insured, and toward the insurer. Philosophically, insurance is a gambling proposition, and if too much information is placed in the hands of one party, the gamble becomes unfair. It is sometimes argued that insurance companies already ask about family histories, and a precedent is therefore established. Quite apart from the question of whether a precedent is always a satisfactory argument for proceeding, it is important to realise that the types of general questions previously asked about family history have very weak predictive power; some genetic tests will have very strong predictive power. The former may be tolerable, where the latter is not—rather as casinos tolerate those with a variety of "systems" for beating the wheel, but would be unlikely to tolerate a precise and reliable method of predicting winning numbers.

It is possible that genetic information may come to have a more positive connotation, if properly regulated, in the context of employment, by allowing the potential employee (and with his permission, the employer) to avoid specific occupational health hazards. For example, those shown to have a particular genetically determined sensitivity to cancer induced by a class of chemicals might be well advised to avoid work situations where they are exposed to such chemicals. This information should not be used to justify general employment discrimination against such people, or to cover sloppy work practices, but should have a potential place as part of an overall workplace safety strategy. This is an area which may require legislation.

3.4 *When is population screening for genetic disease appropriate? What factors, such as cost and the availability of counselling and treatment, should be taken into account? How should screening be organised and regulated?*

The Clinical Genetics Society hopes to develop further professional guidelines in this complex area. The fundamental principles of screening should certainly include full prior informed consent (which necessitates adequate counselling provision); subsequent counselling provision, as needed; proper evaluation of the potential costs, benefits, and cost-benefit ratios of the screening programmes suggested. There are various models of screening organisation, and choosing between them requires pilot studies and objective evaluation, rather than *a priori* discussion. It is likely that there is no single optimum model, but that various disorders in different situations will require a multiplicity of screening protocols. Because of the technical, social and ethical complexity of the area, **the Clinical Genetics Society supports the call of others for a central monitoring body to oversee the introduction of such screening programmes, at least until more experience and knowledge has been gained.** The need for some group to be set up soon is underlined by the recent entry of commercial laboratories into this field, offering a post-in service for Cystic fibrosis carrier testing.

3.5 *If screening for a wide range of genetic predispositions becomes routine, how will people be protected from discrimination on the grounds of their genotype? Should they be?*

As discussed under *3.3*, people who have undergone genetic screening should be entitled to privacy of this information, subject only to proper safeguards against them using the information in an unfair or fraudulent way against insurance companies or employers.

3.6 *Would people be well advised to seek genetic information from sexual partners before the conception of children? Are they likely to? Is this likely to change with future research?*

In very limited situations, particularly in families with a clear history of inherited disease, this has already been practised for some time. Since people have long sought financial information, and information on infectious disease, from potential partners before having children, there is no obvious reason why well validated and clearly delivered genetic information should not be similarly sought. It is most important to ensure that there is sufficient knowledge, and counselling available, for the information to be used constructively, and not taken out of context. There are virtually always many more important factors than genetic anomalies involved in the choice of a spouse.

4.1 *What assistance in the treatment of disease or the design of drugs is given by knowledge of the gene(s) associated with a particular disease?*

There are few specific examples as yet, other than the use of specific gene products as therapeutic agents (e.g., Factor VIII for treating haemophilia, erythropoietin). However, knowledge of the gene associated with a

disease gives insight into the biochemistry of the disorder, and it seems highly probable that such knowledge will, at least in some instances, allow new approaches to developing pharmacological therapies.

4.2 *Are there differences, in principle or in practice, between gene and conventional therapy? How might these affect development costs? How will this affect the actual cost of treatment?*

There are not important differences in principle. The actual costs of treatment will, as for conventional therapies, be dominated not by the costs of the actual treatment reagents themselves, but by the need to comply with safety regulations and by the recouping of development costs by the companies marketing the therapies. It is too early to make specific predictions in any of these areas.

4.3 *To what extent do factors such as technology-transfer facilities, patent protection and regulation influence the commercial exploitation of research findings?*

The Clinical Genetics Society and its sister professional societies in the field have issued a statement on patenting, a copy of which is appended. *We remain opposed to the patenting of natural gene sequences.* We recognise and welcome the need for proper patenting provision for specific applications, or derivatives of gene sequence invented by people for particular purposes, in order to encourage commercial investment in genetic diagnosis and therapy.

4.4 *How does the regulatory regime for genetic-based industry in the United Kingdom compare with that in other countries? Is there a danger that investment will be lost to other countries with different regulations or with better venture capital funding potential?*

It is common experience that small biotechnology companies funded by venture capital, providing the development of medical applications of genetics, and providing services to research teams in these areas, are much more common and well developed in the United States than in the United Kingdom. This may lead to long term adverse economic consequences for the United Kingdom.

4.5 *What products, other than medical diagnostics and therapies, might be produced as a result of human genetic research?*

The phrase "medical diagnostics and therapies" is already so broad as to encompass virtually all of medicine. Parallel genetic research in other organisms will have useful results in agriculture, which will in turn have major consequences for human health. The same is true of research into the genetics of microorganisms pathogenic to Man and domestic species.

5.1 *Why is it worthwhile to map and sequence the human genome? What are the relative advantages of mapping expressed genes only versus complete sequencing the genome?*

Mapping the human genome, and sequencing parts of the genome, are the means of acquiring genetic knowledge. There is no other obvious road to this information. The discussions on relative advantages of mapping expressed genes versus the whole genome concern technical tactics in attempting to acquire the basic genetic information. It is not yet clear which will be the most efficacious strategy.

5.2 *What will it tell us about the human species and the individual that would not otherwise accrue from piecemeal studies?*

This information can only accrue from genetic studies. Current genetic studies are indeed "piecemeal", in the sense that there is not a global scientific strategy with different parts of the work allocated efficiently to different individuals, but rather a loose collaboration. The essence of this collaboration is the early and free interchange of detailed information, via computer databases, which minimises the extent of unnecessary duplication of scientific work.

5.3 *To what extent are human characteristics determined by the genome and to what extent does the environment influence the expression of genes?*

Human characteristics derive from a combination of genetic and environmental influences. The extent to which these dominate varies from one particular situation to another. This variation in the relative contribution of environment and genetics (often expressed as a number called "heritability") does not apply only to a particular trait, but also to the specific situation in which it is being studied. For example, in a (theoretically) entirely inbred strain of mice, variation in a characteristic must of necessity be due only to environmental influence, since the animals are genetically identical; but in a normal outbred wild population of mice, the same trait may show a different range of variation due to both genetic and environmental factors.

5.4 *How much is understood about the organisation of coding information in the genome? Is it conceivable that interventions such as those produced by gene therapy might have unforeseen effects?*

A great deal has been learned about the organisation of coding information in the genome, but in recent years a significant number of entirely unexpected new principles have also come to light, such as: the presence of

genes embedded within other genes; "imprinting", a phenomenon whereby genes are switched off as they pass from parent to child, and remain so for the whole of that child's lifetime; mutations which "progress" by expanding a short sequence; and others. It is conceivable that other such principles of genetic organisation are yet to be learned. It is therefore also conceivable that gene therapy might produce mutational effects due to disruption of some of these mechanisms, although considerable experience gained with animal experiments has not so far validated these concerns. It will be important to proceed cautiously with gene therapy, and to monitor its effects for many years.

5.5 *Is the financial support for research in human genetics adequate when compared with the results which may flow from it?*

The United Kingdom is relatively underfunded for biomedical research in general, and not particularly for research in this individual area. The increasing emphasis on research with short-term benefits leads to shortages in trained researchers in currently unpopular areas, which become bottlenecks when those skills then return to demand. This has happened in mathematical genetics, and in protein chemistry.

6. Evolution

It is by definition extremely difficult to know the pace at which current evolutionary change is progressing, but it is axiomatic that the potential for evolutionary change always exists in a living species. Factors such as environmental change (and changes in social organisation are only one form of environmental change) will influence the direction and speed of evolutionary change. Evolution occurs in response to so many factors, of such complexity, and at such a slow rate, that it is virtually impossible to predict with any confidence the effects of current activities on its progress. Medical procedures such as selective fertilisation or termination are unlikely to have any practical effect on evolution. For example, although the termination of fetuses with severe medical abnormalities may indeed be an extreme form of "discrimination", the great majority of the disorders for which selective termination of pregnancy is practised are not in fact compatible with a normal reproductive future. From an evolutionary standpoint, what matters is whether or not an individual passes their genes to the next generation. The evolutionary consequences of early termination of pregnancy are equivalent to those of a long, but childless, life. Evolution is a blind and imperfect response to the current environment, within a range of available genetic options; and stochastic events play a major role in its early stages. No currently conceivable clinical interventions would have much impact. We should not ignore today's human suffering, because of theoretical assumptions, which cannot be validated, concerning centuries to come.

Memorandum from the National Consumers Council (HGC85) (December 1994)

We welcome this opportunity to submit comments to the Select Committee's enquiry into the ethical, regulatory social and economic issues raised by human genetics research. Due to the technical complexity, as well as the somewhat speculative nature of human genetics research, we have restricted comment to limited areas where we believe a consumer view might prove helpful.

Human genetics research unfolds the inherent variability of human beings. In genetic terms we are clearly not all equal. On the other hand, social development moves towards the goal of allowing us to *act* as if we were all equal. The issues raised by the Science and Technology Committee straddle, uneasily, the zone between these two evolving streams.

Introduction

(i) Most of the National Consumer Council's (NCC) work on genetics has concentrated upon genetic modification programmes and food use.[1] [2] [3] [4] [5] The concentration upon *human* genetics research raises issues, as yet undiscussed, for Council scrutiny. As a result much of this response, prepared in order to meet the Committee's deadlines for submission, focuses on issues of principle, rather than on empirical evidence. Nonetheless we believe that some of the consumer issues raised by the rapid advances in gene technology are sufficiently far reaching to register an early expression of concern. The National Consumer Council hopes to conduct further research into some of these issues in 1995.

(ii) We start a short section on the principles used to assess how consumers may be affected by developments in human genetics research. We then address four of the areas outlined in the Committee's accompanying "Questions" paper:

— General ethical and regulatory.

— Public awareness and education.

— Genetic disease.

— Economic benefits.

Annex 1 sets out a summary of our views, with appropriate cross-references.

(iii) One of the issues raised in the report of the Nuffield Council on Bioethics[6]—the impact of genetic research on employment practice—falls outside our remit, and will not be discussed directly in this response.

HOW WE BEGIN OUR POLICY WORK—THE CONSUMER PRINCIPLES

(iv) The National Consumer Council, like many other organisations, has been grappling with the complexity of issues arising from biotechnology, of which developments in human genetics research are an important part. We do not generally get involved in discussion of ethical issues, such as the fundamental questions about genetic modification. We do however have views about the safety of such developments, the need for information, licensing requirements, and access to products developed through gene modification programmes.

(v) The way we decide which debates to leave alone (because they involve ethical or cultural issues) and which ones we may legitimately contribute to is important. Council tries wherever possible to distinguish between issues that are strictly "consumer" oriented, and those which are more closely related to a person's role as a "citizen". The latter is more likely to throw up questions of ethics, while the former raises practical issues about access and equity to services and goods. Often there may be conflicts and overlaps between the two roles of consumer and citizen, and the interest of the "consumer" may not necessarily prevail.

(vi) Our starting point is the definition of "consumer" as everybody in society in one part of their life: that is, as the purchaser or user of goods or services, whether privately or publicly supplied. We are guided by our Articles of Association, giving us the duty to *"insist that the interest of all consumers including the inarticulate and disadvantaged are taken into account."*[7] Council interprets this as giving us a particular duty to represent the interests of inarticulate and disadvantaged people.

(vii) Looking at the way goods and services are provided to consumers, we often use these key consumer tests:

— *Access:* can people actually get the goods or services they need or want?

— *Choice:* is there any? And can consumers affect the way goods/services are provided through their own decisions?

— *Safety:* are the goods or services a danger to health or welfare?

— *Information:* is it available, and in the right way to help consumers make the best choices for themselves?

— *Equity:* are some or all consumers subject to arbitrary or unfair discrimination?

— *Redress:* if something goes wrong, is there an effective system for putting it right?

— *Representation:* if consumers cannot affect the supply of goods or services through their own decisions, are there ways for their views to be represented?

(viii) Applying these criteria for goods and services provided by the private sector is fairly straightforward. They are also applicable for public provision of goods and services, provided we accept the premise that these will be heavily influenced by public resources. Allocation decisions should be based on equity—there should be no arbitrary discrimination between individuals.

(ix) Distinguishing between "consumer" and "citizen issues" is not straightforward, and it is worth looking at some examples of how the two may interact (Table 1).

TABLE 1

Examples of policy areas with both "citizen" and "consumer" impacts

Policy area	How this might affect us as citizens living in society	How this might affect us as consumers (of goods and services)
The rights and duties of citizens	Holding identification cards with blood group data	Freedom of information issues; data protection laws
The distribution of power in society	Types of information employers may demand from or about, their employees	Ownership under patent of genetically-derived data; consent to medical procedures (e.g., by minors)
Distribution of resources in society	How far should society contribute through tax, to the care of the elderly, sick, unemployed, or disabled?	Third party access to personal data; or cost-benefit and genetic *screening* programmes[1]

[1] The distinction is made here between genetic *screening* as a process of looking for a particular marker to see if it is there (such as screening the UK population for the cystic fibrosis gene), and genetic *testing* in which there is sufficient evidence to indicate that a genetic marker is likely to be present, and hence the likelihood of developing a particular genetic condition (for example Huntington's Disease).

(x) Sometimes it is possible, even helpful, to lump issues into "citizen" and "consumer" camps. On other occasions we are forced to concede that "this is a citizen issue which leads us into consumer territory", and vice versa. The subject under investigation by the Science and Technology Committee—human genetics—leads us in to many of these "grey" areas. Yet it is also one where the short-term "citizen" issues may recede in importance when compared with some of the longer-term implications for the day-to-day lives of consumers.

1. General ethical and regulatory issues

1.1 Our principal objective must be to ensure that the rights of the consumer—and in some instances the *generality* of consumers—are protected. Many "protections" such as the use of ethics committees to sanction research protocols, or professional codes of conduct, may not be adequate when measured against the potential losses faced by an individual when things go wrong in the area of human genetics research. Some legal protection already exists—for example data protection law, medicine licensing requirements, anti-discrimination legislation—though their applicability to aspects of human genetics research has yet to be established. Discussion and debate about genetics generally and genetic screening in particular, appears to be taking place when the basic ground-rules for consumer protection have not yet been *identified,* let alone established. **As a precursor to further work in this area, a legislative review would be an important adjunct in pointing out potential loopholes in consumer protection, as well as setting the scene for further work.**

1.2 The Nuffield Council on Bioethics produced an innovatory and much-needed report on genetic screening,[6] which has received little public discussion and debate. One of their recommendations (10.20, p. 93) calls for the establishment of a central co-ordinating body for the review and monitoring of genetic screening programmes. We would certainly wish to comment on the constitution and remit of any such body. However, the report does not consider in detail the question of who, or what, will monitor and review other applications of human genome research,

- Therapeutics.
- Clinical trials.
- Intellectual property issues.

and the wider social and economic implications of developments in this area:

- Development of genetic registers.
- Use of genetic data by third parties.
- Consent issues, and the status of minors.

1.3 There are many interests involved in these areas—legal, medical, manufacturing, consumer, citizen, ethical, and political. Similarly there are currently many bodies and associations that would need to be consulted and involved in future developments. **While there is merit in a multi-sectoral approach, it may be more efficient, as well as cost-effective, to establish a single "human genome" authority, that is statutorily accountable, and can command public confidence.**

1.4 While this unified approach has merit, cost considerations would be involved. It may be that an existing, statutory body could take on an extended role, provided this was reflected in an increased level of funding. Three issues of principle stand out:

- **Statutory controls**—human genetics are complex, often highly technical, and multi-sectoral in their scientific ramifications. It may well be necessary to establish rules that incorporate the universality achieved only through legislation (for example safeguarding of genetic databases, and effective

sanctions for wrongdoing); on the other hand, we recognise that this is an area of rapid development, and it may be necessary to have a system that is initially flexible and which could serve as a test bed for legal requirements. Benefits and risks of each approach would need to be the subject of consultation.

— **Transparency and accountability** should underpin every element of any coordinating body's work; in particular, procedures for membership, constitution and remit should be fully transparent, and the lines of accountability made explicit; and

— **Representativeness and balance**—membership of any centralised or coordinating body should be representative of all interests, with clear criteria for lay representation *at every level.*

1.5 Perhaps one of the most immediate issues to be addressed is **what does, and what does not, constitute consent either to a clinical procedure, to the release of information to third parties, or for those under the age of 16 and hence legally unable to give informed consent to a procedure**. This is particularly crucial when, as at present, individuals *cannot* be fully informed and counselled about all the consequences of their decision, because many of the outcomes are not known. Ancillary information—for example a list of existing approaches to this problem in other cultural, social or religious backgrounds—could help.

1.6 Around 2–3 per cent. of all couples are at risk of having a child with an inherited disorder[8]. Even when children are apparently healthy, most parents are highly vulnerable to any suggestion that some aspect of their child's development is not within the "normal" range of expected variation. "Normal", that is, for the population in which the child grows up. This vulnerability of parents, plus a poor knowledge of genetics can lead to exploitation by those with vested interests—whether commercial, religious, or indeed, from within the family network itself. One investigation currently underway in the United States is examining use of recombinant human growth hormone in children *other than those whose small stature was due to hormonal causes.* These children did not lack growth hormone—they were just small for their age. The use of the drug in this context is *cosmetic.* It exposes minors to potential longer-term health risks involved in taking a drug when it is not *clinically* required. Use of the drug in this way breaches the approved and licensed indications, as well as being a violation of the Federal Food, Drug and Cosmetic Act of the USA.[9] [10]

1.7 It will be necessary to bear in mind that *social pressures, plus possible resource constraints on the monitoring of medicines, could increase "off licence" use of new genetic treatments, for cosmetic rather than clinical purposes. Central monitoring and very clear treatment protocols may be one answer to this. It may also be necessary to review the current resources available for enforcement activities.*

1.8 It might be argued that access to such treatments should be a matter of informed choice, and that there is little difference from an individual seeking cosmetic surgery to alter physical characteristics. *There is a possibility that treatments developed to tackle a specific genetic condition may be demanded (and used) by consumers* **other than those for which the treatment was licensed**. *This would raise issues of safety, and should things go wrong later, of access to redress.*

1.9 It is presumed here that genetic-based treatments will be subject to the same licensing criteria of efficacy, quality and safety required currently by new pharmaceutical products. Unfortunately it seems that at present in some countries there is a lack of clarity around the licensing of so-called "vectors"[1] and modified cells used for gene therapy. We echo the question raised in *The Lancet*[11]—**when should cell products be considered drugs (and regulated accordingly), and when not?**

1.10 A recent report from Professor Cano and the French commission on gene therapy predicts that by the year 2010, almost 30 per cent. of all healthcare expenses in Western countries will stem from the gene therapy area[12]. This is only 15 years away, raising concerns about the provision of health care. For example:

— **How far will the extension of genetic testing and genetic screening actually increase** *demand* for and use of health services? Testing for affected foetuses could have impacts on the demand for termination services; it could also have a longer-term psychological health problem for women making such a choice, and for their partners.

There may initially be demand for testing for a predisposition to certain cancers (breast, ovarian, colon, prostate). Even supposing this became more widely available, it seems unnecessarily brutal to offer individuals access to such test when medical science currently has little to offer in terms of preventative treatment. Skilled counselling will be required both pre- and post-testing should a joint decision to proceed with testing be made. Similarly those identified at high risk of cancers with strong genetic component, may require regular screening programmes. Not only are these time and resource intensive, but some (such as for colon cancer) may prove fallible in terms of the actual effectiveness of the screening methods used.[13] It is therefore significant that in a recent statement on the use of genetic testing for presymptomatic identification of cancer risk, the US National Advisory Council for Human Genome Research said:

[1] We understand this to mean the way in which the required 'new' genetic material is transferred into the human cells that function inadequately without it. Viruses have the ability to infect dividing cells, and certain types of virus have been modified to act as the necessary 'vectors' for new genetic material. Researchers must balance the need to ensure that the virus replicates rapidly when in the target cells, while making sure that it doesn't kill off too many of the host cells (thus making the patient worse).

"Until more information is available to address [these] critical issues, it is premature to offer DNA testing or screening for cancer predisposition outside a carefully monitored research environment."[14]

It therefore seems unduly optimistic to think that preventive services (such as screening and testing) will be cheaper than treatments, at least in the short and medium term (see also 2.7.1).

— **Will targets for the NHS drugs budget be able to absorb the costs of new gene therapies without a significant increase**? At the moment the medicines bill represents around 10 per cent of the overall NHS budget, and is already subject to significant review and reduction. Patent protection issues (see 4.1, 4.2), plus the current use of the Pharmaceutical Price Regulation Scheme (PPRS) ensure that manufacturers in the UK can charge prices for therapies and medicines that reflect the costs of development. It is not clear how the cost of new therapy involving patented gene vectors could be easily absorbed within projected health budgets. This is a matter of real concern to consumers, and needs debate.

2. Public awareness and education

What is the extent of knowledge of and interest in genetics among different sectors of the public. Should steps be made to improve this and, if so, what form should they take? [**2.1**]

2.1 Even without statistical data to support the assertion, it seems fair to comment that on average, public knowledge of genetics is extremely poor. The science element of the National Curriculum should provide basic education, although it is not until Level 7 that pupils may begin to see the direct relevance of human genetics to their own lives. This also requires an ability to calculate and understand odds such as the probabilities involved in inheritance. These concepts are not readily grasped by the majority of people. Without a reasonable understanding of the concept of personal risk, genetic counselling is more likely to generate anxiety than, as is intended, to guide individuals in decision-making. Thus a grasp of basic science, biology and mathematics will help an individual put genetic information into an understandable context.

2.2 Basic education can help. However, it is clear from the experience of organisations such as the Cystic Fibrosis Trust, the Haemophilia Society, or the Down's Syndrome Association that a personal imperative often drives people to acquire a level of knowledge that previously, they would never have imagined possessing. **If it is agreed that the basic level of knowledge of genetics and heritability needs improvement, then conventional "educational" methods may not be the answer. Genealogy and the history of family traits could have an important role here in popularising what is currently a specialised area of science.**

2.3 The technical complexity of human genetics research is very apparent. This in itself is a barrier to greater consumer involvement and understanding. The language used does not help. In 1989 we said:

"The language of genetic manipulation in fact tends to fall into one of two extreme categories—either the highly technical language of the scientist or the highly emotive language of the propagandist. There is an urgent need for the general public to be informed about genetic manipulation in language which avoids reference on the one hand to eukaryote-prokaryote genetic exchange, and on the other to scientists playing God and tinkering with the stuff of life."[15]

Five years later, these comments are still applicable. Despite the efforts of the Nuffield Council on Bioethics, little progress appears to have been made. **Information expressed in neutral, non-technical language is crucial if consumers are to appreciate and assess the potential benefits and drawbacks of human genetic research.** Without this it is unlikely that they will be able to draw the basic distinctions necessary to play a part in the unfolding debate, let alone exercise informed choice.

2.4 Following on from the need to improve knowledge and understanding of human genetics, it is crucial that this knowledge is placed within a social and cultural context. Without this context, individuals will not have sufficient information to assess the possible outcomes.

2.5 A useful way of viewing risk on an individual level is to consider that it " . . . *is not only the probability of an event, but also the probable magnitude of its outcome., and everything depends on the value that is set on the outcome*".[16] It could be argued that insufficient consideration is given to the differences in attitude to outcomes, that exist between "ordinary" consumers and the clinicians who guide their health care. Prenatal screening for genetic disorders and neural tube defects is a case in point. Clinicians recommend screening in order to detect disease, while women will attend in order to seek reassurance. The difference may seem semantic. It is not. A pregnant woman attending for testing may be asked to decide whether—if the results of her test indicate that the foetus is affected—she will proceed to termination. In other words testing would be offered *only* if women were prepared to terminate an affected foetus. This is not simply speculation. A small survey of obstetricians revealed that around one third thought that women should agree in principle to termination *before* having a test.[17]

2.6 Some of the outcomes will be influenced by a strictly consumerist view—whether the affected individual (and their partner or family) will be able to retain adequate access and choice to a whole range of goods and

services. Our concern is that decisions related to human traits that are made now, or in the near future, *could* have unforeseen consequences.

If we speculate here, take the example of results from a genetic test taken now by an adolescent. Could a negative outcome mean that in 10 years time when they wish to buy a home, they may be refused life insurance—or offered it at terms too high to accept? This may mean a mortgage refusal. These young consumers could be locked out of the home ownership market, which may in turn affect a whole range of life choices (partnerships, families, preferential lending opportunities, investment options). What would happen if this young consumer, again, wanted to provide for their old age and to take up a new form of long-term health care insurance? Would the pre-existence of a genetic trait bar them from exercising such foresight? Or would terms again be too expensive for them to consider? All these aspects need to be considered.

Are there unreasonable expectations of the benefits that might come from genetics? If so, should these be tempered? **[2.3]**

2.7 There is a great deal of debate at the moment on the allocation of resources to health care—often talked of as "rationing". Certainly the outcomes of human genetics research hold potential—and very significant—benefits for individuals and their families. They also pose problems, and a distinction needs to be made here about access to testing and screening, and access to *treatment.*

2.7.1 **Genetic testing** already exists for a number of conditions where a specific gene has been identified as a predictor of disease. Requests for testing have been fairly infrequent, usually from members of a family with a well-known history of a genetic condition (Huntington's disease for example). In addition routine tests for carriers of thalassaemia or sickle cell disease (both of which can cause serious blood disorders) have been carried out since the 1970s among the ethnic groups in which they occur—Mediterraneans and Afro-Caribbeans respectively. However, genetics centres are now receiving requests for predictive tests for a range of other disease conditions[18] (such as Alzheimer's, or some cancers), and physicians are expressing concern about the availability of, and standards for existing counselling programmes. Counselling reduces psychological morbidity, helps those identified at high risk of disease, and is considered essential by geneticists. Their provision will involve increased costs, at least in the short-and medium-term.

2.7.2 **Genetic Screening** also already exists for a variety of conditions. All newborn infants in the UK are screened for phenylketonuria and hypothyroidism, both of which if not detected early enough can lead to irreversible brain damage. Many women will also be familiar with tests carried out during pregnancy for diabetes, and Rhesus haemolytic disease; and in their unborn child, for Down's syndrome, congenital malformations, and some blood disorders. Genetic screening in utero may involve difficult decisions for the mother—and counselling may not always be available, particularly in those health districts where testing is not routinely available on the NHS but is offered privately.[19] This is worrying. We wonder why screening does not appear to be subject to national standards and monitoring (see 2.8 below).

It would be helpful to have more data on the costs and benefits of genetic screening on a population level. A recent paper by Ginsberg and colleagues on a national screening programme for cystic fibrosis in Israel[20] provides examples of the sorts of social and ethical issues that need to be taken into account.

2.7.3 **Genetic treatments**: Without population-specific studies, it is difficult to see how genetic screening programmes, and eventual genetic treatments could be exempt from the current arguments about access to other "premium" and high cost treatments. Typical examples are heart or heart-lung transplants, and in vitro fertilisation programmes. Where will genetic treatments be placed in the hierarchy of clinical needs? A range of "conventional" treatments are available for many genetic conditions and while they are not without side effects and drawbacks, they can improve the quality of individual lives, and extend life span. It is likely that some people will have to continue with these risks and all their attendant disabilities and drawbacks, while others gain access to more radical and effective treatment. If this is to apply to genetic treatments it will have to be explained and justified. This re-emphasises the importance of cost/benefit analysis and population specific studies.

Inequalities in access to health care already exist. Consideration will have to be given to ways in which inequalities in access to new genetic screening and treatment programmes can be minimised. What we do not wish to see is a situation where treatment for genetic disease becomes the preserve of the privileged few, while the remainder are effectively barred from genetic treatment, and the possibility of a better quality of life.

2.8 Consumer expectations will undoubtedly be high, at least initially. It is important that realistic and objective advice and information are readily available from an authoritative source. The consequences of taking forward testing, screening and treatment of genetic conditions will undoubtedly raise individual, family and social dilemmas. Consumer expectations will be tested against whatever is put into place as a "referral and treatment" structure.

2.8.1. Some problems that may emerge without clear national guidelines can already be seen in screening from Down's syndrome, where health districts may choose to offer amniocentesis screening on different

criteria, according to the cut-off values they choose for risk. This means that in some areas the availability of amniocentesis is based on the risks of a 35-year-old woman having an affected child (calculated at 1 in 300)—so more women will have access to the test; other districts may choose to restrict availability of amniocentesis on the basis that around 1 in 150 procedures will provoke a miscarriage. This is both confusing to consumers, and raises the possibility of litigation in cases where one centre refuses amniocentesis while another offers it.[21] **Unrealistic expectations could be minimised, and individual and family dilemmas moderated by the development of a clear national strategy and uniform criteria for the whole human genetics sector.**

2.9 The development of a clearly identifiable, central coordinating body (see 1.3–1.4 above) would support such a national strategy. It such a body is to be truly effective, its boundaries of control, and access to the system of human genetics treatment, need to be very explicitly delineated. One advantage of a statutory system for all aspects of screening, testing, and treating human genetic conditions would be that data are safeguarded. Laboratory standards at genetics centres could be monitored and controlled for quality. Training, skilled counselling, treatment and follow up could be rationalised, and findings disseminated through the coordinating authority.

2.10 The central body could include within its remit, for example, some of the collaborative tasks shown in Table 2.

TABLE 2

The proposed central co-ordinating body for applications of human genetics research: tasks and collaborative partnerships

Suggested tasks:	Possibly in collaboration with:
Basic educational information about genetics	National Curriculum Council with input from health education experts
Patient and family information on gene therapies	Existing, genetic-disease oriented charities, trusts and voluntary organisations
Current research, its status and findings	Medical Research Council and other research funding bodies; plus systematic reviews from the Cochrane Collaboration(s) nationally and internationally
Specific details on referral processes and details of treatment centres	NHS Executive; Royal colleges; Clinical Genetics Society;
Maintain registers of authorised and accredited genetic counsellors	Work with new academic and practice-based centres, illustrated by the M.Sc. in Genetic Counselling offered by Manchester University/St Mary's Hospital
Monitoring and evaluation data on effectiveness, cost and outcomes of treatments	Recognised centres; NHS Executive; Department of Health

2.11 Looking ahead to those individual consumers who may have a personal interest in genetic "treatments", it is important that they understand the "why, when, where, what, who, which and how" of genetic medicine. For example:

- **Why** should I be tested/screened/treated?
- **When** could or should it be done (prenatally; adolescence; at marriage?)
- **Where** will it be done (what centre or hospital has sufficient experience and facilities to treat me?)
- **What** are all the risks involved, for me, for my family and for my future grandchildren?
- **Who,** apart from me, might want to know about the outcome?
- **Which** further treatment options, if any, are available?
- **How** can I get redress if something goes wrong? (if serious consequences arise from either a false negative or positive test; or if a treatment has adverse consequences)

Given our comments about cost implications, an additional important question may be "how much, if anything, will it cost me?"

2.12 Answering these questions places **the emphasis far more heavily, and more correctly in our view, on process rather than strictly on a single outcome (as in the case of the result of a screen or test).** We have assumed that much of the treatment in the future will be at a pre-symptomatic stage. This present very different challenges from current medical practice, when "dis-ease" (in its literal sense) drives consumers to their doctors, and treatment is designed to alleviate specific symptoms.

Individuals will be encouraged to think about their health in a wider psychological, social, and economic context. They are far more likely to be active consumers, in the strict sense of the word, rather than

compliant patients, as many physicians have been trained to see them. Inevitably this must change the whole nature of the medical consultation, and **physicians should be prepared for this as part of their undergraduate training.**

2.13 If individuals initially seeking testing, screening or treatment in this process-oriented way are fully counselled, demand may in fact drop off. One centre offering carrier screening for the cystic fibrosis gene discovered that if people are offered *immediate* screening, over 70 per cent in one study and 95 per cent in another accepted. Only a quarter, however, would make a *return* visit for such a test.[22] This casts doubt on the actual demand for testing, once people have had time to think through implications, and underline the crucial importance of pre-test counselling.

Is there a danger that genetics will be seen as an excuse for socially unacceptable behaviour? Could it be used to justify reductions in social programmes of health, education and welfare? [2.4]

2.14 We are concerned about the long-term impact of advances in gene technology on health and welfare policies, such as disability benefits, pensions, and both publicly- and privately-funded healthcare. Hudson[23] and others[24] have argued that existing and ongoing polices do not take adequate account of "contingent events" (of a negative nature) that face growing numbers of people as they age. We believe that the argument could be extended to human genetics, in that it can be argued that **genetic disease is one of the contingencies that people should not be expected to protect themselves against.**

2.15 The problem that arises over time is the question of whether and if desirable, how to include genetic factors in contingency insurance—both privately supplied or publicly funded. In other words, how much protection should be provided (or not) against a particular set of events will depend upon the *value* set upon the negative outcome and hence the actuarial calculation of risk. As we have said before, this value is likely to vary according to the individual, social, economic, financial or legal perspective taken. The situation is complicated by the fact that there is more than one time-frame to consider, as the effects of gene therapy will be inter-generational. This is discussed further below.

3. Genetic disease

Should information about an individual's genome be regarded as confidential or should it be possible for employers, insurance companies etc., to require genetic tests or to obtain the results of previous tests on an individual or their relatives? [3.3]

3.1 We are not able, at this stage, to comment formally on the impact of genetic tests on sectors such as the financial services industry and the services they offer to consumers. We hope to address this issue in a more comprehensive study in the coming year. However, there are some general points we wish to raise.

3.2 Much of the terminology surrounding both human genetics and financial services needs clarification and explanation. For example, at present **the market for health insurance permits the exclusion of coverage for future expenditures related to pre-existing medical conditions. Where do genetic conditions fall in the spectrum of such conditions, particularly if the individual is pre-symptomatic?** Will unaffected carriers of genetic conditions be required to reveal this information (for example unaffected mothers who pass on the haemophilia gene to some of their sons)? What about those genetic conditions that are triggered into expression by external (environmental) factors such as an unrelated viral illness, exposure to a noxious substance, or pregnancy? Will these be covered by exclusion clauses? We foresee tremendous difficulties unless such—admittedly high complex—issues are the subject of both professional and public debate.

3.3 NCC has already raised concerns[25 26] about potential problems of access to affordable medicines for certain categories of consumer. This problem of equity may be exacerbated by the complex interplay of human genetics, risk and the actuarial calculations of insurance underwriters. Risk, of course, is the actual business of insurance. **However, it seems likely that the applications resulting from human genetics research may, over time, affect the "ceiling" of risk in underwriting terms so that high and moderate risk consumers are screened out. This may mean an increasing pool of uninsurable consumers.**

3.4 Insurance is based on risk assessment. Genetic testing is an extension of the analysis of risk which has always existed as a precondition for insurance, as with medical reports. To the extent that testing results in a more accurate assessment of risk, third party access to information about an individual's genotype could produce a class of people who are virtually uninsurable in terms of life insurance or related products, such as long mortgages. What this may demonstrate ultimately is the limitation of a completely commercially-based insurance system, as the logical outcome of accurate risk assessment will be to exclude certain types of people (or genotype) entirely.

3.5 The health insurance sector is at present fairly small—at 31 December 1993 there were 3.3 million private medical insurance policy holders in the UK, and a total of 6.58 million people covered by private medical insurance.[27] In the main this benefits those with acute episodes of illness, and those who require elective surgery. In a review of European statistics on waiting lists and health care provision, *Laing's Review of Private*

Healthcare concludes that " . . . *the NHS experience of waiting for elective surgery remains as powerful an incentive as ever for buying private medical insurance.*[28] What might happen if a proportion of those seeking private health care (for example in order to take up elective surgery options) were turned down? Or offered premiums they were unable to afford, as a result of genetic conditions?

3.5.1 Third party access to genetic information may mean that more people than at present would be *wholly* dependent upon publicly provided health care. The trade-off is that insurance companies would take less risk and make more profit, while the public health services could be forced to take the brunt of long-term and chronic disease costs. This could increase demand on health services and on longer-term community care provision, in turn feeding through to exert pressure on national health and welfare budgets.

3.6 We could speculate along similar lines for other insurance sectors. **What might happen if life insurance risk ceilings were raised? What impact might this have on the availability of mortgages? Might sections of the population considered to be at risk from genetic conditions be effectively shut out of the private owner-occupied housing market because they are not eligible for—or cannot afford—life cover?** Would this ultimately reinforce social inequality and restricted opportunities in lifestyle—through no fault of the individual, and beyond their power to control?

3.7 One of the NCC's concerns is for individuals who might be discriminated against as a result of their genetic makeup (genotype). There may also be a distorting effect on the insurance, housing, and health markets, the effect upon competition, and an increased burden on all consumers in their role as taxpayers.

3.8 The insurance industry argues that it is entitled to know the result of a test and to take account of it, but remains comparatively silent on the immense difficulties (and flaws) in the actuarial calculations required to assess such risk. How do they take account of the possibility of false negative or false positive test results? They also argue that genetic tests are no different from any other medical test forming part of an insurance policy contract. This is open to challenge (see 3.11, below).

3.9 At this stage, and looking at the balance of risks, it appears that an undue burden of adverse consequences could be carried not only by affected individuals but also their *current and as yet unborn families,* should genetic information be accessible by third parties. Such consequences extend beyond the merely personal (as might be argued in the case of release of information about smoking behaviour, or other health markers), having social and cultural impacts as well as financial and economic. **Information about an individual's genome is unique. Until such time as convincing evidence is available to deflect potential harm and minimise discrimination and stigma, it should have maximum protection—as a reflection of its uniquely private status.**

If not, why is genetic testing any different from current medical tests?

3.10 Geneticists make the distinction between "monogenic" tests and "polygenic" tests, partly because of the comparative ease with which the former can be identified and used in predictive testing. Polygenic conditions, on the other hand, allow for a range of variability, depending on the types of gene sequencing present. Thus breast cancer can have a genetic component but only around 5 per cent of actual cases of breast cancer can be attributed to a specific gene (possession of the so-called BRCA1 gene complex). It is therefore far more difficult to predict the course of the disease and its outcome than it is with monogenic (single gene) conditions. Small errors in testing and analysis can have disastrous consequences for the individual consumer.

In light of uncertainties, plus a lack of public consultation and debate, it seems reasonable that data arising from all "genetic" tests and screens be given the same strong protection in law, until such time as a proper study of consequences for individuals and social groups has been undertaken.

3.11 Genetic testing differs from other medical tests in a number of ways:

— Genetic disease is transmitted vertically, not horizontally; this raises questions of inter-generational equity on social, economic and financial grounds that do not arise in conventional medical tests; the consequences for family members are *both* horizontal (immediate) and vertical (future).

— Because of the vertical transmission, information on one affected individual can also reveal private details about other family members, who may suffer discrimination as a consequence.

— Many genetic diseases are hardly influenced by the usual environment; therefore unlike other types of illness, major lifestyle changes could have little effect on the eventual course of the disease.

— Because recurrence of specific genetic disease can be predicted with far greater accuracy, its presence in a family, or a cultural group, or a population can become a social stigma (for example Tay-Sachs disease in Ashkenazi Jews).

— The *presumption* of genetic testing appears to be that the presence of a specific marker or gene has adverse consequences for the individual, who is therefore in need of treatment or "modification" in some way. This may or may not be the case, depending on the condition (see below).

If screening for a wide range of genetic predispositions becomes routine, how will people be protected from discrimination on the grounds of their genotype? Should they be? [3.5]

3.12 For some conditions individual gene treatments may be life-saving (where expression of the gene is effectively lethal—such as in Huntington's Disease); and/or certainly life-enhancing—for example for haemophilia or diabetes. The case is not so clear for other conditions—colour blindness, for example, or long- and short-sightedness. Judgments made about which genotype is "normal" and which "abnormal" are heavily dependent upon the environmental, social, cultural and economic conditions in which individuals find themselves. This places an adverse connotation on what evolutionary biologists might see as potentially beneficial genes complexes, under different environmental stimuli.

3.13 Public and social perception of human genetic research has probably been unduly influenced by its close association with "medical" research, and its insufficient emphasis on the immense and natural variability of human beings. The *benefits* this variability gives us have been less emphasised than the problems and risks such variation *may* create. Somehow, and the NCC has no easy answers here, a less judgmental and more positive balance needs to be struck between the two.

3.14 Should genetic screening for a wider range of genetic predispositions become routine, then there are dangers of stigmatisation and discrimination, even if such screening is voluntary. We have already touched upon the subtle pressure for termination of affected foetuses (see 2.5 above) as an example of social and medical attitudes. For many parents termination is not an option they wish to consider. Combined with the incidence of spontaneous mutation this will mean that there will always be a proportion of individuals in a community and a population who show evidence of genetic conditions. For such families and children, there are many dangers, including:

- Social disapprobation for what could be seen as "irresponsible" reproductive choices (*"You brought your troubles on yourself . . . "*).
- Pressure to ignore the special needs of families with genetic conditions (if conditions become rarer through successful screening programmes, demand for special services may fall, leading to less willingness to provide them in the first place).
- Down-grading of research into conventional medical treatments for genetic conditions (there will always be a need for this).
- Reduced access to services—financial, special education, or mobility related (due to third-party access to information on an individual's genotype).

The strongest possible measures should be taken to safeguard individuals, families and socio-cultural groupings from inequitable and socially divisive discrimination on grounds of genotype.

3.15 In terms of active protection of individuals, families, and socio-cultural groups, other social and organisational processes will have to be involved. For example, it will be necessary to develop specific lines of referral, treatment and follow up particularly as there will be a need for inter-generational monitoring of patients and their families. Clearly the type of data being generated by genetic programmes will require scrupulous care in use and storage. This can best be done when there are a minimum of "data leaks" from the overall system, and may well be best met by establishing a limited number of authorised centres of excellence, overseen and monitored by a central co-ordinating body.

4. Economic benefits

To what extent do factors, such as technology-transfer facilities, patent protection and regulation, influence the commercial exploitation of research findings? [4.3]

4.1 Patents will protect intellectual property and—in the area of pharmaceuticals for example—allow the manufacturer sufficient time to recoup the costs of development. Consideration of how this may or may not benefit consumers does not really enter into the initial equation. Nonetheless, a careful balance needs to be struck between the *risks* of monopolistic pricing, and the *benefits* of protecting and encouraging innovative research from which consumers will ultimately benefit (see 2.7). There is some evidence that the exploitation of a monopoly position may be a crucial issue to be tackled in the area of human genetics:

- **How can a single patent be granted to a manufacturer when the vast majority of the work contributing to the application has been collaborative? Is a review of patent law needed?** This is true of human genome research more than any other area, where free and open co-operation has been an unusual feature of much of the research.
- **What effect will patenting have upon the likelihood of future research into a particular area?** For example, research into hepatitis C virus (HCV) is urgently needed. There are worrying signs that the enforcement of a patent on the virus itself, made as a result of the development of a "virus-testing" kit, has already discouraged others from continuing work in this important field.[29 30] Similar problems are emerging with the BRCA1 (breast cancer) gene, which is also being patented by a single interest. Researchers cannot afford to run the risk that their work might result in massive

law suits for patent infringement on the one hand; on the other, if licence fees were paid, it would make the results of such research prohibitively expensive—and well beyond the budget of most health care services.

4.2 How might end-users be affected by macro-economic policies and intellectual property law? These will have an impact on the cost price, and it is foolish to pretend that cost considerations do *not* play a part in the provision of medicines—they do. We have previously referred to instances of restrictions on the use of erythropoeitin (in patients with chronic renal failure).[31] We could also point to debates about the use of more expensive high purity and/or recombinant Factor VIII in the treatment of haemophiliacs (which may carry a lower risk of adverse reactions), compared with the lower cost of dried heat-treated products.[32] All these debates will accelerate as more genetically-derived products are marketed. Public discussion and debate of these issues should be a priority, and should be in consultation with user groups.

4.2.1 Access to more expensive new medicines such as those produced by gene technology will be subject to an increasingly refined screening process. **The criteria for such screening, and how these are arrived at, are seldom made explicit—either to patients or to service providers. They should be.**

References

[1] National Consumer Council: *Genetic modification programmes and food use. A statement to the MAFF Study Group on Genetic Modification Programmes and Food Use.* PD03/93.

[2] National Consumer Council: *The labelling of foods sourced from genetically modified organisms. Response to the Food Advisory Committee's Revised Guidelines.* PD17/93.

[3] *National Consumer Council: The genetic manipulation of plants, animals and microbes. The social and ethical issues for consumers: a discussion paper.* Roger Straughan. August 1989. PD20/89.

[4] *Your Food: Whose Choice?* edited by the National Consumer Council. HMSO, London. 1992.

[5] National Consumer Council: *The ethical implications of emerging technologies in the breeding of farm animals.* Letter to the Biotechnology Unit, Ministry of Agriculture, Fishers and Food. 16 March 1993.

[6] *Genetic Screening—Ethical Issues.* Report of the Nuffield Council on Bioethics Working Party on Genetic Screening. Nuffield Council on Bioethics, 1993.

[7] Memorandum and Articles of Association of National Consumer Council. Incorporated 25 March 1975. Re-issued in July 1991, and amended in line with statutory instruments coming into effect after 1975. National Consumer Council: PD17/P/91.

[8] Report on Screening for Genetic Disease. Royal College of Physicians, London. 1989,

[9] See for example: "US drug firm to be quizzed over growth hormone". *British Medical Journal* Vol. 309. 3 September 1944. p. 559.

[10] "FDA investigates Genentech's involvement in growth charities". *Scrip* No. 1952. 26 August 1944. p. 8-9.

[11] "Co-ordination of gene therapy in France". *The Lancet.* Vol. 344, 26 November 1994. p. 1494.

[12] See reports: "French present gene therapy plan". *Scrip* No. 1982, 9 December 1994, p. 6.

[13] Lang, C A and Ransohoff, D F: "Fecal occult blood screening for colorectal cancer. Is mortality reduced by chance selection for screening colonoscopy?". *Journal of the American Medical Association,* 6 April, 1994. Vol. 271, No. 13. pp. 1011-14.

[14] "Statement on use of DNA testing for presymptomatic identification of cancer risk", by the National Advisory Council for Human Genome Research. *Journal of the American Medical Association,* 9 March, 1994. Vol. 271, No. 10. p. 785.

[15] Straughan, Roger: *The genetic manipulation of plants, animals and microbes. The Social and ethical issues for consumers: a discussion paper.* National Consumer Council. August 1989. PD20.89. pp. 33-35.

[16] Douglas, M: "Risk as a Forensic Science". *Daedalus* (1990); **119**: 1-16.

[17] Unpublished survey data, cited by Professor Malcolm Ferguson-Smith at a Genetic Screening Symposium, Centre of Medical Law and Ethics and Nuffield Council. 22 March, 1994.

[18] Letter from Sheila Simpson, John Dean and Neva Haites: "Genetic prediction of adult onset disease". *British Medical Journal* vol. 308, 19 February 1994. p. 535.

[19] Letter from Patricia A Boyd: "Serum screening for Down's syndrome. Private patients may receive less counselling". *British Medical Journal* Vol. 309, 19 November 1994. p. 1372.

[20] Ginsberg G, Blau H, Kerem E *et al*: "Cost-benefit analysis of a national screening programme for cystic fibrosis in an Israeli population". *Health Economics.* Vol. 3: 5-23 (1994).

[21] Letter from Reynolds T and John R: "National policy would ensure consistency". *British Medical Journal.* Vol. 309, 19 November 1994. p. 1373.

[22] Marteau, T: "Screening for carriers of cystic fibrosis. Psychological consequences are unclear." *British Medical Journal.* Vol. 309. 26 November 1994. pp. 1429-30.

[23] Hudson, Robert A: "Social Contingencies, the Aged, and Public Policy". *The Milbank Quarterly.* Vol. 71 (1993): 2. pp. 253-77.2

[24] See also for example: 10 Have, Henk and Louglin, Micheal: "Responsibilities and Rationalities: should the patient be blamed?" *Health Care Analysis* Vol. 2 (1994); pp. 119-27.

[25] For example see, National Consumer Council: *Pharmaceuticals. A consumer perspective.* PD42/91. December 1991. p. 65.

[26] National Consumer Council: *Consumer perspectives on the NHS drugs budget. Memorandum to the Health Committee Enquiry.* PD36/93. October 1993. p. 1, 12.

[27] *Laing's Review of Private Healthcare 1994.* Laing and Buisson Publications, London. p. 138.

[28] See above, pp. 156-57.

[29] See for example: "Your life in their patent". Independent. 5 December 1994.

[30] "Patent rights and HCV tests". *The Lancet,* Vol. 344, No. 8937. 10 December 1994. p. 1632.
[31] See for example: *Scrip* 1521, 8 June, 1990. p. 4.
[32] See for example, Hilgartner M W, Buckley J D *et al*: "Purity of factor VIII concentrates and serial CD4 counts". *The Lancet* (1993); **341**: 1373-74, and subsequent correspondence.

ANNEX 1

Summary and broad conclusions

We follow the broad categories set out in the Committee's briefing. The bold type refers to the relevant section of this paper where a more detailed discussion is set out.

General ethical and regulatory issues

As a precursor to further work in this area, a legislative review would be an important adjunct in pointing out potential loopholes in consumer protection, as well as setting the scene for further work [1.1, p. 4].

While there is merit in a multi-sectoral approach to monitor the applications and outcomes of human genetics research, it may be more efficient, as well as cost-effective, to establish a single "human genome" authority, that is statutorily accountable, and command public confidence. [1.3, p. 5].

Such a central body should embrace three important principles.

— Statutory controls.
— Transparency and accountability.
— Representativeness and balance [1.4, p. 5].

Multi-sectoral discussion is needed on what does, and what does not constitute **consent** either to a clinical procedure; to the release of information to third parties; or for those under age of 16 and hence legally unable to give informed consent to a procedure [1.5, p. 6].

Social pressures and possible resource constraints on the monitoring of medicines could increase "off licence" use of new genetic treatments, for *cosmetic* rather than clinical purposes. Central monitoring and very clear treatment protocols may be one answer to this. It may also be necessary to review the current resource available for enforcement activities [1.7, p. 6].

Treatments developed to tackle a specific genetic condition may be demanded (and used) by consumers *other than those for which the treatment was licensed.* This would raise issues of safety, and if things go wrong later, of redress [1.8, p. 6].

Should *all* cell-based genetic tests and therapies be considered as medicinal products (within the meaning of the Medicines Act 1968), and regulated accordingly? [1.9, p. 7].

How far will the extension of genetic testing and genetic screening actually increase *demand* for and use of health services? [1.10, p. 7].

Will the NHS drugs budget be able to absorb the costs of new gene therapies without a significant increase? [1.10, p. 8].

Public awareness and education

Conventional "educational" methods may not be the solution to improving basic levels of knowledge of genetics and heritability. Genealogy and history of family traits could have an important role here in popularising what is currently a specialised area of science [2.2, p. 9].

Information expressed in neutral, non-technical language is crucial if consumers are to appreciate and assess the potential benefits and drawbacks of human genetic research. Without this it is unlikely that they will be able to draw the basic distinctions necessary to play a part in the unfolding debate, let alone exercise informed choice [2.3, p. 9].

Resources should be allocated to ensure that adequate numbers of fully-trained counsellors are available [2.7.1, p. 11].

It would be helpful to have more data on costs and benefits of genetic screening on a population level [2.7.2, p. 11].

Inequalities in access to health care already exist. They are likely to be further emphasised by high-technology (and by deduction, high-cost) developments in medicine [2.7.3, p. 12].

Unrealistic expectations could be minimised and individual and family dilemmas moderated by the developments of a clear national strategy for the whole human genetics sector [2.8.1, p. 12].

The emphasis in genetic medicine should be placed on *process* rather than strictly on a single outcome (as in the case of the result of a screen or test), in order that human genetic issues are seen in their correct perspective—as one part in the process of human, social and cultural diversity. [2.12, p. 14].

Development of genetic treatments (especially at presymptomatic stages) may mean that individuals will think about their health in a wider psychological, social, and economic context. They are far more likely to be active *consumers,* in the strict sense of the word, rather than compliant *patients.* Physicians should be prepared for this as part of their undergraduate training. [2.13, p. 14]

Genetic disease is one of the contingencies that people *should not be expected to protect themselves against* [2.14, p. 15].

Genetic disease

The market for health insurance permits the exclusion of coverage from future expenditures related to pre-existing medical conditions. Where do genetic conditions fall in the spectrum of such conditions, particularly if the individual is pre-symptomatic? [3.2, p. 16].

It seems likely that the applications resulting from human genetics research may, over time, lower the "ceiling" of acceptable risk in terms of insurance underwriting. This may mean an increasing pool of uninsurable consumers, and increasing pressures on state provision of health, housing and welfare benefits. [3.3, p. 16]

For health insurance, a far greater number than at present could be *wholly* dependent upon public provision of health care. This will exert an upward pressure on government health budgets. [3.5.1, p. 17]

What might happen if life insurance risk ceilings raised? What impact might this have on the availability of mortgages? Might sections of the population considered to be at risk from genetic conditions be effectively shut out of the private housing market because they are not eligible—or cannot afford—life cover? [3.6, p. 17]

Information about an individual's genome is unique. Until such time as convincing evidence is available to deflect potential harm and minimise discrimination and stigma, such data should enjoy the maximum protection—as a reflection of its uniquely private status. [3.9, p. 18]

In light of uncertainties, plus a lack of public consultation and debate, it seems reasonable that data arising from all "genetic" tests, screens and treatments be given the same strong protection in law, until such time as a proper study of detrimental consequences for individuals and social groups has been undertaken. [3.10, p. 18]

Public and social perception of human genetic research has been unduly influenced by its close association with "medical" research, and its insufficient emphasis on the immense and natural variability of human beings. The *benefits* this variability gives us have been less emphasised than the problems and risks such variation *may* create. A better balance needs to be struck. [3.12, p. 19]

The strongest possible measures should be taken to safeguard individuals, family and socio-cultural groups from inequitable and socially divisive discrimination on the grounds of genotype. [3.14, p. 20]

Economic issues

How can a single patent be granted to a manufacturer when the vast majority of the work contributing to the application has been collaborative? Is a review of patent law needed? [4.1, p. 21]

What effect will patenting have upon the likelihood of future research into a particular area? Treatment of disease is an evolving science, the progress of which could be seriously hampered if patenting of gene sequences is not assessed in its wider (global) context. [4.1, p. 21]

Access to more expensive new medicines such as those produced by recombinant gene technology, will inevitably be subject to an increasingly refined selection process. The criteria for selection and how these are arrived at, are seldom made explicit—either to patients or to service providers. They should be. [4.2, p. 21]

Consumers are entitled to information about what precisely is being done in genetic manipulation work, as they may be unaware that it could conflict with their religious or moral beliefs. In addition, they should have the right to choose not to buy products which result from these techniques and processes. [4.3, p. 21]

Memorandum from Dr R Turner (HCC88) (5 January 1995)

I enclose:

(1) A Paper I read to last Years annual Health Computing Conference in Harrogate (Organised by the Health Service Journal and the British Computer Society).[1]

(2) A selection of articles from various sources mentioning the word "Insurance" in relation to either Genetics or HIV (given that the two present very similar ethical problems).[1]

(3) A few articles demonstrating how "Confidential" records held on computer files can go amiss.[1]

A major problem is that so many people could claim to have a legitimate "Need to Know" about patient records. A person with Huntington's disease (inherited as an autosomal dominant genetic disorder) for example will be looked after by many professional staff in both hospitals, General Practices, at home and in NHS or Private nursing homes, not to mention Social Security staff etc.

Paper medical records may be difficult to read and impossible to analyse using a computer but they *do* have the advantage that they are difficult for people to access without anyone being aware, and they tend only to have a limited amount of information in them. An insurance company executive, for example, would have to write to a consultant to obtain information from hospital case notes since he would find it difficult to just walk into the medical records department and start searching along the files. Paper based records similarly do not come under the provisions of the Data Protection Act so the patient cannot demand a copy as of right. Lastly, the fact that they are often handwritten and full of abbreviations makes them difficult for the outsider to read.

NHS Computer systems, on the other hand, are now being designed to collect information about patients from the cradle to the grave. They neatly file, categorise, and code every detail and will make it available to "Authorised" users over the network which brings me back to the first point—who *exactly* will be authorised (and by whom ?)?

I am the chairman and/or a member of a number of committees (national, regional, and local) dealing with the establishment of networked computer systems in the NHS and would be pleased to discuss what might be done about all this with the Select Committee if they would be interested.

Memorandum from CRC Technology Ltd (HGC89) (9 January 1995)

Section 4: Economic Benefits

4.3 *"To what extent do factors such as technology transfer facilities, patent protection and regulation influence the commercial exploitation of research findings?"*

Broadly, the commercial exploitation of research findings in human genetics falls into three categories of products or services:

(a) Screening and prophylaxis

(b) Diagnosis

(c) Therapy

Whereas screening and diagnosis maybe achieved relatively quickly following gene identification, the route to therapeutic products is a far more costly and long-term venture. For both technology transfer organisations and the industry alike, commercial exploitation in therapy is a very different business from that for diagnosis and screening.

That being said, it is easy to succumb to an over-emphasis of the mystique of human genetics and commercial exploitation. Many of the current rules and practices will still apply. At this stage however, some of the main difficulties are an inability to accurately value research findings and intellectual property, an un-trodden route in the steps from gene discovery to therapeutic drug and a lack of precedent or case history with regard to patents and cross-licensing.

Thus it may be too early to attempt to answer the topic posed in this question until we have some illustrative examples to refer to. Nevertheless, in CRCT we have for more than seven years been involved in the identification, protection, development and scale of new cancer drugs to the biotechnology and pharmaceutical industry and from our recent interactions with the Wellcome Trust, there are clearly a few special characteristics pertinent to technology transfer and human genetics.

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[1] Not published.

1. In any technology transfer project it is important at the outset to sort out and pull together matters such as the ownership of intellectual property, the structure and management of collaborative research with industry, and the development of an appropriate patent strategy downstream.

In human genetics, it is apparent that the first of these, the ownership and identification of intellectual property is particularly complicated. This derives from several factors including:

— Multi-family studies, funded by several research organisations and involving several participating groups, (often overseas).

— The importance of know-how in analysing genetic data and the difficulty of putting a value on this.

— The need to maintain the freedom of research groups to exchange materials without damaging the position of an industrial sponsor or collaborating partner.

2. Secondly, it is interesting to note how far back in the drug-to-market pathway we are in the human genetics kind of deal compared to CRCT's more usual drug licensing activities.

If we look at this in a very simple step-wise fashion then the steps are these:

1. Collect family material.
2. Identify markers.
3. Identify genes.
4. [? identify gene function?].
5. Establish whether the gene offers a therapeutic target for intervention.
6. Establish how to intervene.
7. Design, make or otherwise find candidate drugs.
8. Develop and evaluate in pre-clinical studies.
9. Phase I clinical trials.
10. Later development and clinical evaluation.

In conventional drug discovery and from CRC-funded research programmes, an interaction with industry at Step 8 in the pathway would be deemed early (and risky, since neither party has much idea of the value each of them brings to collaboration) and it would be quite normal for CRCT to seek an industrial partner only at Stages 9 or 10 of the pathway when we are much clearer what we have to offer, what is needed to turn it into a drug and what its value is. How much more difficult then will it be to structure agreements and license deals for interactions between academic groups and industry at Step 1. This is a matter to which we are currently giving much thought.

3. A further complicating factor is the potential scope for commercial exploitation which a key gene sequence may offer and whether indeed any one company is sufficiently well-placed and well-motivated to maximise the usefulness of the information to which it may hold exclusive rights. On the other hand, a policy of non-exclusive licensing or too much carving up of fields and territories can reduce the commercial value of the property in question such that no one finds it an attractive target for commercial development. For those of us whose objectives are to ensure maximum public benefit derives from research findings the need to find the right balance in these matters is a crucial question.

4. Last but not least, of course are the complexities of filing for patent applications in relation to human genetics. It is not my intention to delve into this much-debated topic here but suffice it may be to note a few pertinent points:

(a) There may well be reason for technology transfer groups and academic organisations to file for patent applications to protect their own positions irrespective of how the industry exploits these downstream.

(b) The time-lag from gene discovery to drug launch obviously questions the value of filing claims for therapeutic intervention, since these may well have expired before the drug reaches the market.

5. Ethical, moral and social issues are of much greater bearing than more conventional patent applications emanating from medical research.

6. It is difficult to postulate on the generality of the scope of claims which may be granted or cross-licensing deals done.

7. The speed of progress, and the importance to academic groups of being first to publish on gene sequences make publication and presentation of data paramount. These can not be held up by patent filing procedures.

QUESTION 4.4

I am sure there are others better qualified to answer this question than me but I thought I would just comment on the reference to venture capital funding and perhaps the implication that this is the key restriction to start-up ventures in the UK compared to other competitors.

I think it is unrealistic not to acknowledge that the USA will always be ahead in the start-up arena for the conceivable future but this relates to a variety of cultural factors not just the availability of VC funding. Nevertheless the divide between the UK and USA is far less now that in the late '80's for a variety of reasons:

— More difficult now to raise VC in the USA.

— Trans-Atlantic investments.

— The UK is more open to start-ups than 7-10 years ago.

I would be interested to know what is happening in Japan in this respect. I think very little and it may be that like the development of the biologicals industry, the Japanese majors will merely explore inter-company deals at a later stage. This activity has been quite extensive recently in the USA, and is something it may be useful to explore in planning future policy.

Finally—a key factor which may contribute to differences in the derivation of commercial benefit in the UK and USA may come back to the continuing difference in patent law. In a field which moves as quickly as human genetics, the USA dominance of "first to invent" over "first to file" may be critical.

Memorandum from The Huntington's Disease Association (HGC90) (9 January 1995)

The Huntington's Disease Association is a voluntary organisation committed to the care of families affected by Huntington's disease. The Association exists to give support and advice to families, to help raise awareness of their needs and to educate the caring professionals, politicians and the general public into the nature of the disease. We welcome your inquiry into human genetics and the opportunity it gives us to make a contribution to your deliberations.

Huntington's disease is a degenerative neurological disorder with a dominant mode of inheritance. The disease may begin in childhood or old age but the onset is usually in the early forties. The illness is characterised by involuntary movements, loss of motor control and dementia. It is progressive and death occurs after 10-20 years. Presymptomatic testing has been available by linked marker for 10 years, but because of the discovery of the defective gene in March 1993 a direct gene test is now available. Over this period we have learnt much that we hope will be both useful and relevant to your inquiry.

Genetic Testing/Screening

There are many benefits in genetic testing when a disease is treatable but benefits are less clear cut when there is neither treatment nor cure and onset is late. However testing allows for informed choice about parenthood, helps in decision making on lifestyle and allows for preparation for future economic and practical difficulties. It can also bring peace of mind even when it shows the defective gene to be present. However, there are limits to the information revealed. Present technology cannot reveal age of onset or likely severity but it is probable that in the future the answers will be available with all the attendant difficulties.

Genetic testing/screening may allow for informed choice about parenthood but the choices are between difficult options with a late onset disorder. If you have first accepted the premise that you do not want to pass on the defective gene you have to then choose between aborting a fetus who might have enjoyed perhaps 40 or 50 years of healthy life or foregoing parenthood. Also if one of you knows that you carry the gene, you have to question whether it is fair to have children who may have to witness their parent's relentless physical and mental deterioration. With widespread media attention given to the concept of "designer babies" and the screening of all pregnancies for certain defects parents who produce children with disabilities or with the possibility of future genetic disease often feel stigmatised. With the ever growing number of genes being discovered that indicate a predisposition to certain conditions, we must be aware of the dangers of seeking perfection at the expense of individuality. In a society where disabled people are already disadvantaged the constant striving towards the elimination of the so called "abnormal" must constantly erode their self worth.

Informed consent

A most important criterion of genetic testing or screening is informed consent. Genetic counsellors stress the importance of helping a person understand what is involved and to what they are consenting. But genetic disease is about families. There will be family members who will receive information by default. Their informed consent is not required or sought.

Confidentiality

Confidentiality is essential if the autonomy of the individual is to be maintained. But genetic information is relevant to the lives of other family members. There will be circumstances where it is felt that the individual's right to control of the information should be overridden. In Huntington's disease problems have been encountered where a person wanting a predictive test has a grandparent affected by the disease but a parent who is healthy. If the test shows that the person has inherited the gene, the parent must also have it. Therefore you have given information to an adult child and have changed the status of the parent from a 50 per cent risk to a 100 per cent certainty. As an Association we believe that an individual has a right to know his status but we have to consider the concerns of the parent and the right not to know. This has obvious relevance to genetic screening programmes where the individual must retain the right not to participate. In both the areas of informed consent and confidentiality it is important that high professional standards are maintained.

Employment

Many employers already require a medical examination and may in future request access to genetic information. There is financial benefit in the exclusion of employees who become ill because of a predisposition to a work related illness, or whose future illness might result in an impaired performance. Predictive tests could become part of standard health checks thereby disadvantaging people who would in all likelihood have made a useful contribution in the workplace. As an Association we believe that in the event of an employer receiving genetic information, either by disclosure on an application form or through screening, it should not be used to exclude people from employment unless a condition had already developed to a degree where performance would be impaired. There should also be a responsibility on the part of the employer to have sufficient competence to interpret the information correctly.

Insurance

Experience to date in Huntington's disease has shown that people at risk of developing the disease are insurable. There are companies who have developed detailed knowledge of the disease so that they can make meaningful judgments without excluding applicants from access to insurance. However, this experience is not general. Many people have come to our Association after failing to find a sympathetic hearing. Obviously once you have received a positive predictive test or you have developed symptoms of the disease you become uninsurable. There would be greater problems than those that exist now if pensions and healthcare provision were to be provided by private insurance rather than taxation. Government policy is placing greater emphasis on the importance of individual provision. In these circumstances methods of assessment of risk would perhaps become more rigorous—genetic profiling could become a part of it and protection would be removed from those who might need it most. We believe that the advances in the field of genetics should not be used to unfairly exclude individuals from the insurance market with all the resulting social implications. A dialogue should be entered into with the Association of British Insurers to ensure that fairness prevails.

Genetic counselling

As more diseases are shown to have an inherited element the pressures on such services will be immense. Huge resources will be required if the kind of support that has proved effective in Huntington's disease is to be made available—the support is not just about predictive testing—it should include a follow up service to include the support of the entire family. We are concerned that if services are not expanded to accommodate the burgeoning caseload commercial laboratories will be set up to provide genetic testing without the all important counselling services.

Education and public awareness

We believe that genetics should be given a high profile in school education and welcome the inclusion of genetics in the national curriculum. We feel that a better knowledge about genetics will help prevent misunderstandings and general anxiety about research in the field. Education and public awareness will help safeguard against any possible excesses that could occur in research. It is important for the general public to contribute to the debate on the ethical issues raised by scientific advance.

Patenting

We are of the opinion that it should not be possible to patent a gene as it is not an invention. It has been said that patenting rewards invention and stimulates innovation but in the case of genes there is no opportunity for

betterment. We believe that laws intended for physical devices are inappropriate and will inhibit rather than promote medical research. We also realise that commercial laboratories are entitled to a financial return from their investment but do not feel that this should extend to the patenting of genes. They should obviously be able to patent any subsequent technology.

Conclusion

The major discoveries being made in the field of genetics bring new hope to all those who suffer as a result of inherited disease but they bring great risks. The Council of Europe's Bioethics Convention on Human Rights and the Dignity of the Human Being has stated that "freedom of scientific research in the field of biology and medicine is justified not only by humanity's right to knowledge, but also by the considerable progress its results bring as far as health is concerned. Nevertheless, such freedom is not absolute. In medical research it is limited by the fundamental rights of individuals—the Convention specifies that its aim is to protect the dignity and identity of human beings and guarantee to everyone, without discrimination, respect for their integrity as well as for other rights and fundamental freedoms". We believe that such ethical safeguards are essential. The alternative could be the creation of a genetic underclass—families disadvantaged in education, employment, healthcare, insurance—stigmatised—the social outcasts of the 21st century.

We thank the committee for affording us the opportunity of giving our views and would be happy to discuss the matters further if you should so wish.

Memorandum from Professor Hiliary Rose, Social Science Research Unit, Institute of Education, and Professor Steven Rose, Department of Biology, Open University (HGC91) (9 January 1995)

We welcome the inquiry of the Committee into this important question, seeing its discussion as part of the process which extends the informed and critical public understanding of science. The questions require an interdisciplinary approach and we have therefore submitted this evidence jointly, reflecting our different expertise in the life and the social sciences. HR is a sociologist of science who has made a study of patient's understanding of their genetic disorder as part of the ESRC Public Understanding of Science programme; SR is a biologist who has led the Open University genetics courses which have been used both by individual students and by university teaching departments over a number of years.

1. General ethical and regulatory

1.1 Aspects of this question which more specifically concern the nature of gene action are covered in more detail in 5.3 below. The salient points with respect to use and regulation are that with the exception of a small but very important number of conditions in which a single change or defect in a gene leads seemingly almost inexorably to a specific outcome in terms of a phenotypic "character", most aspects of the human condition of clinical or social importance in which genes have any part to play are the results of the interactions of many genes in complex environments. Therefore predictive statements about the likelihood of a particular combination of genes identified in an individual or a foetus leading to a particular outcome are always at best only statistical, and as always, the provision of such information is not neutral in that it itself changes outcomes (parents being told that their child carries genes which "may predispose" towards schizophrenia are likely to treat that child differently and hence for better or worse affect that outcome). The major area of scientific ignorance is a lack of the conceptual tools to deal with complexity; the developmental rules governing the route from the single dimension of DNA to the five dimensions of the human individual (three of space, one of personal life history and one of social and cultural context) are largely unknown and relatively under-researched.

1.2 Management of research on the ethical and social consequences of the new genetics is inappropriately allocated to the MRC, which is the body responsible for managing the genetics programme itself and thus has insufficient independence to sponsor basic social science research with the potential to raise difficult questions about the cultural and social implications of the new genetics. Instead it is predisposed structurally to commission only "handmaiden research", that is, social research subordinated to the programme and whose purpose is to smooth out problems of acceptance. Acceptance research cannot answer the kinds of questions currently being raised by the public and by politicians about the new genetics.

There are further, more technical objections to the programme, as the MRC has a particular history as a funder of social science research, primarily psychology, and has an over-strong commitment to quantitative work. By contrast the US ELSI project has more independence from the biomedical establishment and has funded important qualitative studies which have been able to explore some of the more difficult questions. Fortunately

the ESRC is using some of its Risk project to support qualitative research on the cultural impact of the new genetics.

Appropriate management of the ethical, legal and social issues (which we would hope would include both economic and *cultural*—the latter regrettably missed in the terms of reference of POST) should be carried out with the ESRC as the lead commissioning agency, recruiting ethicists through the British Academy and geneticists through the MRC. Another possible location would be the Science Policy Support Group which has appropriate expertise to commission the necessary empirical research through a range of disciplines (for example in running the successful Public Understanding of Science programme). Much more such empirical research is required if ethical and policy debates are to be fed by systematic knowledge rather than mere abstract speculation.

British social sciences have a strong place in international STS studies and could play a leading part in shaping European ELSI research. This will need locating with greater independence from the biomedical establishment and will need additional funding (in the US ELSI gets 3 per cent of the genetics budget). In Europe the parliamentarians successfully fought for a similar ELSI element to genetics funding within Framework IV.

Lastly the foundations are playing a part: Nuffield is active in ethics research, while Wellcome has so far put a rather modest £100K into the public understanding of genetics. It would be helpful if Wellcome were to play a similar role in supporting social research in the new genetics to that they have played in the context of AIDS.

1.3 The question is misconceived. It is not a question of moral prohibition, but of determining effective priorities in the allocation of resources. For example, in the US some $400 million is currently allocated to a Federal Violence Initiative originating in a proposal by the then Director of the NIMH, Frederick Goodwin, to identify at least 100,000 inner city children whose alleged perinatal and genetic defects will make them violence-prone in later life. Yet no genetic explanation can account for instance, for the 154 per cent increase that has occurred between 1985 and 1991 in the rate at which young men aged between 15 and 19 are being killed in the US. There may be rare genes which may in particular contexts "predispose" their possessor to particular forms of behaviour that result in violence, but research aimed at finding solutions to the major social problem that violence currently presents in the US by focusing on the genes is an ineffectual allocation of public monies rather than immoral, except in the more general sense that such manifest misallocation precludes other more effective responses.

1.4 This question has two aspects, the first about the relationship of genetic explanation to culture, and the second about the limits to genetic explanation and the claims of determinism. It is however not a new debate; it has recurred in each generation at least since Darwin's day, in the polemical disputes over the explanatory powers of sociobiology in the 1970s and 80s and currently in the debates around IQ and the "underclass." What is new is the way in which the mystique of the new genetics is seen as strengthening the determinist argument. At its simplest, genetic determinism argues a directly causal relationship between gene and behaviour. A man is homosexual because he has a "gay brain," itself the product of "gay genes" and a woman is depressed because she has genes "for" depression. There is violence on the streets because people have "violent" or "criminal" genes; people get drunk because they have genes "for" alcoholism.

(a) This renewed Social Darwinism is most strongly articulated from within the US and the debate then imported into Britain, because currently the US is both world leader in the new genetics, and is also passing through a severe social crisis. The political classes seem to have lost confidence in finding social solutions to social problems, which continue to deepen, not least in terms of the very high levels of incarceration, particularly of black men. In this context scientific claims, whether well or illfounded, for a genetic explanation of behaviour are often amplified by press and politicians, as they offer justification for the inability of the political process to tackle hard social problems.

It is important to be aware of the role of a number of leading geneticists in sustaining the renewed Social Darwinism of the last two decades. Social research has offered a more critical view of the stereotype offered by elite spokespeople for science in which the modest scientist makes only scientific claims which are then traduced by an irresponsible media. Instead academic scientists have been shown to actively collaborate with PR staff to put out press releases about their work which are hyped to attract media attention and through this to position themselves to compete for scarce research funds. The "gay gene" story was paradigmatic in this respect; it was actively sold to the media so that religious leaders, gay activists and other self appointed ethicists publicly commented on the social implications of a finding which was in itself unreplicated, immediately contested in the technical press and, as offering at best a "marker" for a gene rather than a gene, a long way from producing anything like a diagnostic measure. How the public is to see through the moral fog generated by this self inflation by scientists and ethicists becomes a problem in itself. Good investigative journalism and social science studies are needed to make visible the social processes which research based on short-term grants increasingly seems to require.

(b) The naive genetic determinism which characterises much of this debate is based on a faulty reductive sequence whose steps include: reification; arbitrary agglomeration; improper quantification; spurious localisation; misplaced causality; and dichotomous partitioning between genetic and environmental causes. Reification converts a dynamic process into a static phenomenon. Thus violence, rather than describing an action/ activity between persons, or even a person and the natural world, becomes instead

a "character"—aggression—a thing which can be abstracted from the dynamically interactive system in which it appears and studied in isolation. The same process occurs with "intelligence," "altruism," "homosexuality," etc. Yet if the activity described by the term violence can only be expressed in an interaction between individuals, to reify the process is to lose its meaning.

Arbitrary agglomeration carries reification a step further, lumping together many different reified interactions as all exemplars of the one thing. Thus aggression becomes the term used to describe processes as disparate as a man abusing his partner or child, fights between football fans, strikers resisting police, racist attacks on ethnic minorities, civil and national wars. All are assumed to be manifestations of some unitary underlying property of the individuals, so that identical biological mechanisms are involved in, or even cause, each.

Improper quantification argues that reified and agglomerated characters can be given numerical value. If a person is violent, or intelligent, it offers to measure how violent, how intelligent, by comparison with other people. The history of the IQ scale and its manipulation is well known in this context. The quantification of "aggression" is also interesting in that it illustrates another feature of the reductionist cascade which leads to genetic determinism, an animal model. Place an unfamiliar mouse into a cage occupied by a rat, and often the rat will eventually kill the mouse. The time taken for the rat to perform this act is taken as a surrogate for the rat's aggression; some rats will kill quickly, others slowly or even not at all. The rat which kills in thirty seconds is on this scale twice as aggressive as the rat which takes a minute. Such a measure, dignified as *muricidal behaviour,* serves as a quantitative index for the study of aggression, ignoring the many other aspects of the rat-mouse interaction, for instance the dimensions, shape and degree of familiarity of the cage environment to the participants in the muricidal interaction, whether there are opportunities for retreat or escape, and the prior history of interactions between the pair. And just as time to kill becomes a surrogate for a measure of aggression, so this behaviour in the rat is transmogrified into drive-by gangs shooting up a district in Los Angeles.

Having reified processes into things and arbitrarily quantified them, the reified object ceases to be a property even of the individual, but instead that of a part of the person. So the penchant for speaking of, for example, schizophrenic brains, genes—or even urine—rather than of brains, genes or urine derived from a person diagnosed as suffering from schizophrenia. Of course, everyone ought to know that this is a shorthand, but the discourse once initiated does more than sell books for their scientific authors; it both reflects and endorses the modes of thought and explanation that constitute genetic determinism, for it disarticulates the complex properties of individuals into isolated and localised lumps of biology and encourages naive policy proposals.

It is at this point that genetic determinism introduces its misplaced sense of causality. It is of course probable that during aggressive encounters people show dramatic changes in, for instance hormones, neurotransmitters and neurophysiological responses, all of which can be affected by drug treatments. People whose life history includes many such encounters are likely to show lasting differences in a variety of brain and body markers. But to describe such changes as if they were the causes of particular behaviours is to mistake correlation or even consequence for cause (aspirin may alleviate a headache, but the cause of the ache is not too little aspirin in the brain).

1.6 As in many UN issues this has a crucial South/North dimension. The overwhelming Human Rights issue which the UN is uniquely placed to address is the prioritisation of the rights of survival of indigenous peoples over and above the collection of samples of their genomes. To preserve the scientific record of a people whilst permitting their virtual extinction comes distressingly close to a replay of Nazi science. The second Human Rights general principle which the UN needs to articulate is respect for and protection of human genetic diversity. Issues of privacy, genetic discrimination and prohibiting germ line manipulation are important themes which will more immediately affect peoples from the North; national and other supranational bodies, both governmental and NGOs will have well thought out positions on these reflecting differing cultural and political contexts. Inevitably any UN strategy will be at a high level of generality and will run into the usual problems which inhibit their ratification by nation states.

2. Public awareness and education

2.1 The question is to be welcomed in that it acknowledges that "the public" is composed of very different groups with different educational needs. Yet there is a sense that because of the content of genetics that this is an area in which there is general need for public awareness. Here technical knowledge and ideas of a good society fuse, in that what genetics does is to underline diversity between people. Positively this can lead to a shared pleasure in and a willingness to care for human biodiversity or it can sustain genetic discrimination and the creation of non-citizens. Many geneticists argue that the new genetics is a tremendous argument for the provision of a national health service, as genetic risk can only be managed by pooling. In the US some States have moved to outlaw genetic discrimination in insurance, but such positive developments can only occur if there is a widespread sense of protecting human diversity which parallels the social concern for nature which led to the Rio convention.

In terms of specific groups needing education, there has been a rapid expansion of genetic testing and counselling services within the NHS but it is not clear that the educational base underpinning this Topsy-like growth has been adequately prepared. Key groups include:

(a) General practitioners: It is widely recognised that general practitioners have a weak understanding of both genetics and their social implications, but they form the crucial interface between the patient and a rapidly expanding array of genetic diagnostics. A twofold strategy is needed both to improve medical education and also to provide attractive genetics courses through distance learning to update practising GPs.

(b) Nurses. A very similar argument could be made for nurse education, particularly in midwifery where diagnostic testing may do more to harm rather than calm the concerns of the pregnant woman, and to damage the relationship between the mother and her newborn. Nursing research in this area also needs encouraging.

(c) Service users. Women and their partners who are thinking of having a baby also need reliable information about positive and negative aspects of diagnostic testing. With the increasing medicalisation of birth women need technically well informed social support. This is a particularly delicate area as emphasis on screening for physical and other impairments intensifies the stigmatisation of disabled people, 95 per cent of whom acquire disability post-birth. Many disabled peoples' groups regard such an emphasis on screening out and aborting "impaired foetuses" as eugenic.

(d) The prevention of genetic discrimination in employment and in insurance needs to be tackled through education directed towards the relevant groups: employers' associations, trade unions and professional associations, and the insurance industry. There are welcome signs of interest in these issues and of their coverage in the popular media.

2.2 It is always difficult to discuss anxiety about science as anxiety and excessive trust seem to go hand in hand. Both quantitative and qualitative research point to those with the strongest technical knowledge having the most sceptical view of science. The evidence is that strategies which seek to hide possible risks, for example, not to label BST milk products, are likely to intensify public suspicion rather than to reduce it. The experience of Danish biotech firms (e.g., Novo-Nordisk) in taking the public into their confidence is particularly illuminating; by contrast British industry, which seems to share the national culture of secrecy, is going to have real difficulties learning to be upfront.

2.3 As we have suggested some of the worst offenders in overstating the claims of genetics, are among leading scientific figures. Daniel Koshland, the editor of *Science* (alongside *Nature* the most influential science journal in the world) went so far as to argue that the Human Genome project would solve the problems of schizophrenia, alcoholism and even homelessness. However it is also scientists such as members of the Council for Responsible Genetics (US) or the smaller Genetics Forum in the UK, which have sought to temper these claims.

2.4 Of course this is dangerous, and the key to this question is who is to define socially unacceptable behaviour. The former Chief Rabbi's apparent approval of a possible diagnostic test for homosexuality during the gay gene debate (given that abortion is the only conceivable conclusion) would seem to give tacit support for sexual cleansing. To someone with less homophobic views such a test (even if possible, which remains highly questionable) should be outlawed in the same way that sexual testing in order to terminate female foetuses is in a number of countries. Defending Human Rights is unquestionably going to be difficult as much of the medical thinking about diagnostic testing is couched in terms of saving money on the care of people with impairments.

2.5 Britain, despite the nostalgic longings, is now a profoundly multicultural society; thus if ever there were any "right" questions there are very few now, as concepts of "rightness" are culturally shaped. The relatively new concern with Human Rights expressed in movements all over the world is perhaps the nearest we can approach to such matters, as it offers a way of thinking about the "right" questions in a multi-cultural context. Although it is fashionable to mock "PC" it does reflect a serious attempt to include all those voices in society which have historically been excluded from public policy making, so that the "right" questions have usually been posed (and answered) by economically privileged white men.

3. Genetic disease

3.1 Others will comment in more detail on the organisation and growing delivery of genetic diagnostic services. There is a problem about coverage; for example HR's research found evidence that genetic disorders such as Familial Hypercholesterolaemia with known and effective therapies and which exist in ethnic minorities are not being spotted and sent for specialist advice. On the other hand diagnosing when there is no therapy is ethically quite difficult; the problem is to protect the caring professionalism of clinical genetics from the gung-ho enthusiasts who wish to test out their latest diagnostic measure and then take it to market. The pressure coming from the market as it seeks out new technologies to make and sell must not be allowed to preclude Technological Assessment. The proliferation of unassessed technologies within medicine such as ultrasound scanning in antenatal care, recently criticised by a WHO metaanalysis, must not be allowed to continue.

3.2 Gene therapies coming on line are extremely diverse and the ethical issues that each raises are consequently different. As a generalisation it would be reasonable to suggest that among biologists somatic gene

therapy is not generally seen as radically different from more conventional treatments, but that culturally numbers of people find the idea disturbing and as raising new problems. Recent opinion studies suggest that hostility is diminishing but there are a number of doubts about the relationship of opinion surveys in the abstract to very personal and concrete decision making. On the whole unless there is a major disaster these new therapies are likely to find themselves accepted by many or most, along with the rest of high technology medicine.

3.3 Privacy and the protection of Human Rights will need defending with some sophistication, but again it is important that such regulation is not made only on the basis of such highly publicised and dramatic disorders as Huntington's. The well-documented experiences of the insurance industry and AIDS is not over-encouraging as their desire to diminish the individual firm's risk and retreat from the pool principle has led to negative public health developments and to individual and family distress. In general the example of the US health system with many hundreds of thousands of completely uninsurable citizens through ordinary health checks serves as a warning of how socially negative such genetic developments could be. In a period where there is some evidence of privatisation within the UK health system these developments need sharp monitoring.

3.4 Apart from the ethical consideration that in general no screening should take place where there is no effective and affordable therapy, it would be extremely helpful to have a study of any such already carried out population screening. One US study demonstrated that, including the cost of adequate education and counselling, locating one foetus with a faulty gene for even a relatively common conditions was prohibitively costly. Even then identifying a faulty gene must leave the individual woman to make the ultimate choice to keep or terminate a pregnancy.

3.5 We have talked about the danger of genetic discrimination and see this is an entirely real hazard which needs sensitive but firm regulation and enforcement.

3.6 No anthropological or sociological research exploring how people decide to have children has come up with any evidence that rationalistic risk assessment is part of the process. In HR's study of people with Familial Hypercholesterolaemia, which predisposes to heart attacks and premature death, there was no suggestion from any of the study families that this was a matter for discussion; even engaged couples well aware of the risk status of one of the partners were not taking this into their discussions. We do know of one academic couple with considerable genetic knowledge who both had FH and who decided not to have children as the double inheritance is associated with heart attacks and death of extremely young children. Thus we would make the guess that as the culture becomes more genetically informed, and perhaps if women and men feel less pressurised to have children, decisions about having children will change. Studying how decisions about whether to have children are made by couples who have extensive biological knowledge is likely to offer some illumination to your very interesting invitation to speculate on the future.

4. Economic benefits

4.1 Identifying a gene associated with a particular disease does not of itself provide information relevant to drug design, as even with a single gene the biochemical route that leads from gene to disorder is unclear and the phenotypic condition may take years to develop. However, where it is possible to predict from the identification and sequencing of the gene the protein product for which it codes, there is more therapeutic scope. As protein engineering and rational drug design, based to an increasing extent on computer modelling procedures, become more routine, then gene identification will be helpful. Even in cases which there is a clear genetic involvement in only a fraction of individuals suffering from a disorder (e.g., the 5 per cent or so of Alzheimer's or breast cancer cases) identification of the gene and gene product involved may point the way towards those aspects of metabolism which are also very awry in the more common forms of the condition (e.g., the beta-amyloid protein in Alzheimer's). To our knowledge this is still a promissory note rather than common pharmaceutical practice, but it should certainly not be discounted. However some severe genetic disorders affect only very tiny numbers of families in the population. Directing scientific research to generating therapies for such conditions is unlikely to yield substantial economic gain even granted potential global markets. Such research has to be socially or morally rather than economically justified.

5. Research

5.1-2 Others will doubtless stress the advantages of a coordinated international effort in human genome mapping and will explain the distinction between the original project, which was to sequence the genome (including the 95 per cent + of DNA with currently no known genetic function) and the more rational mapping strategy. Obviously such an approach will not say anything "about the human species" which could not be learned from piecemeal studies, but it will get there faster and the experience of such internationally coordinated approaches to scientific goals will provide useful lessons.

5.3 This "nature/nurture" question reveals the extent to which in popular debate the nature of gene action is still misunderstood. Any individual gene can only be expressed in an environment which includes all the other genes within the genome, and the expression of most genes varies depending on that environment. For some

genes, the range of reaction is markedly dependent on the environment, for others there is very little environmental effect. And with the exception of a number of very important single gene disorders, the overwhelming majority of human characteristics are shaped by a large number of genes acting in concert and in interaction with the environment during development. The shorthand phrase of a gene "for" a condition is profoundly misleading—after all there aren't really even genes "for" blue or brown eyes, let alone such complex historically and socially shaped features of human existence as sexuality or interpersonal violence. The cellular development and enzymatic route which results in the manufacture of particular pigments involves many thousand genes; the route which leads to the types of behaviour we may call violent, for example clearly involves genes, but cannot sensibly be regarded as abstractly embodied in them. What there are, of course, are differences between genomes, genes in the absence of which differences in eye colour or other phenotypes may emerge. The biologist looking at the effects of particular genetic mutations or deletions studies the functioning of the system in the absence or malfunction of a particular gene. Furthermore, the system is not a passive responder to absence or malfunction, but seeks, by means of developmental plasticity, to compensate for any deficit.

A considerable disservice was done to biology by the historical chance which meant that in the early years of this century two separate subdisciplines emerged; genetics, which essentially asks questions about the origins of differences between organisms, and developmental biology, which asks questions about the processes which ensure similarity. The careless language of DNA and molecular genetics services to widen this gap rather than help bridge it so as to open the route towards the synthetic biology that we so badly need. As is well known, chimpanzees and humans share upwards of 98 per cent of their DNA, yet no one would confuse the two phenotypes. We have no idea at present about the developmental rules which lead in one case to the chimp, in the other to the human, but this, surely one of the great unsolved riddles of biology, seems a matter of indifference to most molecularly oriented geneticists.

5.5 The main concern here is the extent to which the human genome project and the prestige and funding that has accrued to it has ring-fenced resources and drawn into itself money and talent that might be better employed in other areas of biological research.

6. Evolution

It seems helpful to begin by sketching out something of the nature of evolutionary processes so as to distinguish between the fact of evolution and the mechanisms which may direct it, notably natural selection. In the questions this distinction is blurred. Evolution in the biological sense simply means change over time, and such change can be described as occurring at a variety of levels from the genomic to the phenotypic. Thus at the genomic level it refers to a change in gene frequencies within a population; at the phenotypic to a change in the frequency of specific "characters." Changes in gene frequencies occur continually as a result of, amongst many other factors, random mutational events. Because there is not a direct linear relationship between genotype and phenotype (see comments above) changes at one level are not necessarily reflected in changes at the other (see the detailed discussion in the evolutionary literature around theories of punctuated equilibrium). Evolution is a feature of all living systems, and occurs in humans just as it does in all other organisms. None of the questions raised in 6.1–6.7 has any bearing on this.

The confusion behind the questions lies in relationship to the *direction* and *mechanism* of evolution. One major but not the only mechanism of evolution is Darwinian natural selection, and it is sometimes argued that human social interventions weaken the processes of natural selection in that individuals who would in the "natural" state not survive may do in modern society, thereby preventing the elimination of the "unfit." But this is a fundamental misunderstanding of what is meant by "fitness;" in the biological sense "fitness" means "fitness in a particular environment". For instance, whilst in the paleolithic environment shortsightedness would be likely to be selected against, in modern societies with the availability of simple technical aids to vision such as glasses, genes which may predispose to shortsightedness are no longer "unfit" in the sense that they do not result in fewer survivors amongst the offspring of shortsighted people. Thus whilst human evolution continues to occur, the nature of the selection pressures which help drive it differ generation by generation.

However this is only a special case (made more striking by the rate of social and technological change over the past centuries of human history) of a general property of evolutionary processes. Environments are always changing, at least in part as a result of the activities of living organisms (the Gaia hypothesis is only an extreme version of this fact), and these changes are not predictable—indeed they are by definition indeterminate. Yet selection can only act in the context of the present environment. Thus evolution by natural selection only ensures increased fitness to the present, not to a future environment and therefore it always follows rather than leads environmental change.

Questions 6.2–6.4 have to be considered within this general framework, the final answer being simply that considered over evolutionary timescales there is no way of telling, though clearly the rate of environmental change which has been dramatically increased by human activity will itself present new and not readily predictable selection pressures.

6.5 Presents a different problem. The specific answer to the question is essentially zero, as the scale on which any such selective fertilisation procedures are likely to be practiced within the foreseeable future, set in

the context of a human gene pool based on a population of six billion or so, is miniscule. However there is good evidence of the effects of selective female abortion and infanticide on the sex ratio of the surviving population in for instance both India and China. At present this constitutes a dramatic example of patriarchal power in male-dominated societies; whether in the longer run, the reduction in the numbers of females, together with industrialisation will force a social and cultural change, increasing the value of females and hence redressing the ratio, remains to be seen.

6.6 The main issue here is speed-up in the context of the unpredictability of simple manipulations of complex systems. The effects of single gene changes in a "natural" population are tested in a variety of ways by selection pressures across environments. Many naturally occurring mutant genes are rapidly eliminated from the population because they prove lethal, often because they cannot survive within the integrated genome that all organisms possess. The new techniques of gene manipulation enable these processes of elimination to be circumvented, partly by protecting the newly inserted genes from the processes that would otherwise prevent them from functioning. Yet the consequences of such gene insertions are almost always pleiotropic (that is, they have multiple effects, frequently unpredictable), and the "natural" (that is complex, and evolved over many thousands of generations) mechanisms that protect populations from the consequences of such mutant genes, which are currently poorly understood, may be circumvented.

6.7 The suggestion that human evolution has been "by sexual reproduction guided by human behavioural drives" is a highly contentious formulation from within biological reductionism. The social science research on why people marry, decide to have or not have children produces a more complex picture in which biological drive is presocial. Indeed members of the Committee in reflecting on their own decisions in such matters may care to consider how far they are acting on simple "human behavioural drives." Such "drives" do not occur in the abstract and so far as one knows throughout human history pairings resulting in offspring cannot be equated to the random pollination which constitutes sexual reproduction in plants. It is to be doubted that clinical interventions are ever significantly going to shape the reasons why men and women choose to have sex and/or to have children in such a way as to alter selection pressures. What such interventions might conceivably do is to reduce the incidence of certain deleterious single genes in the population (thalassaemia is the text-book example), though it should always be remembered that genes which are deleterious in homozygote may in particular environments confer heterozygotic advantage (e.g., the claimed protection against malaria provided by single copies of the sickle cell or thalassaemia genes).

Memorandum from The Society, Religion and Technology Project, Church of Scotland (HGC92) (10 January 1995)

This response is complementary to the one submitted from the study group on human genetics of the Board of Social Responsibility of the Church of Scotland.[1] Whereas that report provides you with a more general response which touches in a relevant way on many of the questions you are asking, this present submission seeks to respond *specifically* to certain questions, and in so doing covers a number of areas which lie outside those being addressed in the study group's report. The two submissions should thus be seen as complementary. Like the study group's report, this submission is not an official statement of the Church of Scotland, since such a statement can only be made by its annual General Assembly. It does however represent the current thinking on these issues by the project of the church which is set up to consider ethical questions in the field of science and technology in general.

THE SOCIETY, RELIGION AND TECHNOLOGY PROJECT

The Church of Scotland has a historic and profound tradition of ethical and social concern in the nation, and remains today one of the largest organisations in Scottish society, embracing all walks of life. It set up the Society, Religion and Technology Project (SRT) in 1970 to stimulate debate and reflection on the ethical issues arising in current and future technological developments. Through working groups it has acted as an effective forum for interaction between experts in a wide variety of fields. Many of these studies have been published and have provided valuable and informed comment. The SRT Project has since December 1993 been running an expert working group is itself engaged in the parallel area of addressing ethical concerns in genetic engineering in non-human life forms. This group is convened by the Project's current full time Director, Dr. Donald Bruce, who is also a member of the human genetics study group referred to above. He was formerly a research chemist in nuclear energy and in energy policy assessment. He also represents the UK churches on a bioethics working group of the European Ecumenical Commission for Church and Society.

[1] Not printed in this volume.

1.2 *Are the current policies being pursued by the MRC and other funding bodies with regard to ethical and social consequences of research in human genetics adequate?*

Response: In our view, biotechnology applied to humans is being treated in too fragmentary and too private a manner for the public good. As biomedical methods have advanced, it has become increasingly apparent that the complexity of the issues leads into profound linkages with many other issues, such as abortion, fertilisation and our concept of what is "normal". The trend to deal with this complexity by separate committees, has in some instances led to the ignoring of issues germane to the subject, on the grounds that they lay outside that committee's brief, when common sense would have seen an obvious connection. In this and other ways, the failure to recognise the interconnectedness of the issues can lead to poor ethical practice.

We suggest that the handling of ethical matters needs to be in the hands of a single, standing Royal Commission on Human Bioethics, separate from the funding authorities, and with oversight of genetic testing, therapy and experimentation, and also human fertilisation and embryology. In the interests of open public debate, its activities should, as far as possible, be undertaken in public, not *in camera.*

1.3(a) *Has society a right to declare that some research topics should be prohibited because they are intrinsically likely to lead to insuperable moral problems?*

Response: Yes, society does have this right, and more serious recognition needs to be made of this point. It has been the subject of criticism by a number of observers that for many years there has been a predominance in Government ethical committees of utilitarian modes of debate, which have tended to marginalise or even exclude the possibility of *intrinsic* moral and ethical objections on the part of many members of society. We regard this as a flawed approach to doing ethics. Most people would say that certain things are intrinsically right (e.g., love and forgiveness) or wrong (e.g., rape or child abuse). Christians (as well as those of the Jewish and Islamic faith communities) have rooted certain moral absolutes in the nature and character of God. We recognise, of course, that there are many difficulties in how to respond to such principles on complex issues, and how a democratic society should legislate among differing principles, but to deny the possibility of intrinsic moral objections would be to override the beliefs of many in society, in a thoroughly undemocratic fashion. Moreover, it can be argued that the presupposition by some ethicists that there can be no ethics of principle is itself a position of principle!

1.3(b) *Should geneticists think more widely than their immediate research goals and their likely consequences or should they leave that to others?*

Response: We could not express too strongly that geneticists should think more widely than their immediate research goals and their immediate consequences. This should not just be left to others. There are three aspects to this.

First, there is an urgent need to educate practising scientists in all disciplines in the need for personal ethical reflection as fundamental to their practice of science in a civilised society. It should be made an intrinsic element in the education of biotechnologists, especially at tertiary level, that they should be taught the rudiments of ethical thinking relevant to their field, and be encouraged to think ethically in the course of their working career. Since the time of the Enlightenment, the dominant mode of doing science has emphasised a reductionist approach, stressing the impartiality and detachment of the scientist, and the danger of personal feelings and judgments being involved. We feel that this has been taken too far, such that the social and moral implications of scientists' work are seen as either improper for their consideration, or at the very least "someone else's job". This is another example of the fragmentary nature of the practice of biotechnology. Sociologists and philosophers of science have long been pointing out that the work of scientific research is itself one where ethical values are fundamentally involved. We thoroughly uphold the need for proper, repeatable experimentation in as reasonably objective a manner as possible, but there are limits to scientists' detachment and objectivity. The very choices of experimental programmes to pursue, the emphases within those programmes, the way that data are interpreted and reported, the choice to publicise or keep secret, etc.—all these are "value-laden" questions.

Secondly, the Society, Religion and Technology Project of the Church of Scotland has over 25 years convened multi-disciplinary expert working groups on many ethical issues arising from modern technology, including one currently considering non-human genetic engineering. It can testify to the value which scientists working in such fields have found in having an opportunity to explore ethical issues alongside experts in ethics, theology, sociology, etc., which they do not have in the normal course of their work. The cross-fertilisation is of especial value. Although many individual scientists do indeed think about the issues, and many discuss them within the circles of their working colleagues, these have the limitations of being largely closed circles. There is much benefit to be gained from the wider perspective of those outside the research or industrial community who are used to thinking about ethics. Such opportunities are currently the exception, but they ought to become commonplace.

Lastly, it is important that geneticists think about the ethical dimension to their work because neither they nor their work are isolated entities but are part of the wider community of society. Since the activities of the scientific research and technological development reside in this community, both locally and nationally, they have a responsibility to that community. Each scientist therefore needs to take this aspect into account in his or

her work. We would draw an analogy with Health and Safety legislation, where the onus is on each person in the workplace to be aware of safety, to adopt safe practices and recognise and avoid unsafe ones. The same idea should apply in the ethical realm.

Pragmatically, it is also in the geneticists' interests to think ethically on their own initiative, if they are to get their next proposal past the relevant ethical committee, and, even more, if they expect the public to support them. In a climate of greater accountability, and of more suspicion of science, those engaged in such work need to have a sensitivity to public awareness.

1.3(c) *Are geneticists pursuing hidden agendas of which the public is unaware?*

Response: Following from the idea that all scientists' work is to some extent influenced by their personal values, world view and goals, then there will always be "agendas". That is simply a normal and unavoidable aspect of being human (see for example Mary Midgley's book "Science as Salvation"). The results are frequently not so much a hidden agenda as an accidental one. Unless he or she has been accustomed or trained to think ethically, a scientist may not be aware of this dimension to their work. This is of some concern, as we have just noted, but what is of more concern is where a scientist, research group, commercial company or even a state has a deliberate agenda, which is not disclosed to the public. Whilst we would not wish to be alarmist over prospects of widespread underhand activities, it would be equally foolish to suppose that these could never exist. The use of eugenic practices by the Nazi regime leaves one in no doubt that scientists and politicians are certainly capable of such agendas, which would nowadays need to be hidden. The commercial world is also no stranger to unprincipled activities in pursuit of profit. The best antidote to such excesses in a democratic society is to create a climate of accountability, openness and awareness on the part of scientists, government and public alike. Such initiatives as the recent UK National Consensus Conference on Plant Biotechnology should be extended to cover human genetics, and also to cover wider regions of the UK than South-east England.

1.4 (a) *Does research into human genetics lead to a deterministic or any other particular view of human behaviour?*

Response: Undoubtedly, there is a danger of exalting the "reductionist" model of human being, as a result of genetic research. This is nothing new, however, and it arises not so much out of genetics *per se,* so much as the imposition of a narrow Enlightenment view on to science, which is then transferred into the realm of philosophy. It is quite proper to describe the mechanism by which a gene "switches on" a protein, which then leads to a particular effect in the body, but quite improper to say that my response was "nothing but" the result of the operation of the gene. The late Professor Donald MacKay referred to this as "nothing buttery". It can lead to many absurd notions about human beings, on the premise that science will tell us the "real" answer. In recent years, many senior Christian men and women of science have pointed to the need for the more holistic understanding view of the human person to which the Bible testifies, where body, mind and spirit are inextricably bound together. In this context, human genetics can provide many advances in our understanding of the human person, since genetics is no longer treated as though it was the true key to our identity, but merely one welcome element in a much wider and deeper picture, some of which is not in the gift of *any* branch of science to determine.

1.4 (b) *Will people try to improve the world through genetic interventions? Should they?*

Response: At a trivial level, of course anyone involved in genetic intervention would surely hope that the world would be a better place as a result, but we presume that because you have a more specific meaning by having posed this question in the context of a question about determinism. Following on from our response to that question, if the reductionist world view were taken, then there is no bar to all kinds of "improvement" of the human species, and presumably thus of the world. Indeed it would suggest that it is our duty to improve it as far as we can endeavour. The more holistic Biblical perspective suggests that there is so much more to the human person than his or her genes that it is ridiculous to speak of improvement by means of genetics. In particular, while human beings and their societies carry the moral taint to which Christian teaching bears witness, merely tinkering with genetics misses the point, since no amount of genetic intervention will make us inevitably better people in either the moral or the spiritual sense. Medical intervention by way of repairing or restoring capacities lost by disease is, of course, thoroughly to be encouraged, and is not in this sense "improvement".

There is also both an absurd and a more sinister aspect to this notion of "improvement". The absurd one is what we should think an "improvement" was, and against what criteria we should determine this. For example, how could we know whether we were not upsetting a balance? The sinister aspect is that of who should determine what improvement was, and how they would set about implementing it. Quite apart from any other reasons, the risk of abuse in this area is sufficient alone to show that there should be a permanent global ban on this area. Again, the Nazi genetic programme testifies to the fact that humans are capable of thinking along these lines and that states can wish to put forward programmes to implement them.

1.5 *Are there other objections to germline interventions? Would this be playing God? What does this mean and why would it be wrong?*

Response: From the previous remarks about the folly and ethical unacceptableness of "improving" human beings genetically, it follows that germline intervention to improve human beings is intrinsically wrong. This is

regardless of the uncertainty of the long-term biological effects and the ethical issue arising from our inability to obtain the consent of the future generations who would be affected. The question of germline therapy addressed to a medical condition is, however, more complex.

The term "playing God" has become somewhat confused by careless use. In a religious sense, strictly it is intended to mean a forbidden action in a province which belongs to God alone—in this case attempting to intervene to change the "given" order of creation. This might be argued as forbidden on principle because it implies man usurping the place of God, and forbidden in consequential terms because human beings could never be said to have anything remotely comparable to divine wisdom in knowing how to intervene. Hence the analogy is made with children playing at being adults, while lacking the knowledge and experience to make adult decisions. In a Christian context, we would agree that to take it upon ourselves to "improve" human beings genetically would be a wrong sense of playing God, as it would also be (even supposing it were possible) to create genetic chimeras which were half human and half animal. To do so would be to take to ourselves God's role of *creator* far beyond any sense for which the Bible would give warrant. However, there is a sense in which gene *therapy*, to restore our genetic condition by correcting a defect, could be said to be "playing God" in a right sense of reflecting (on a limited scale) his *saving* activity for humankind. This in the same way that any other medical intervention has a "redemptive" aspect about it, in so far as it models the healing activity of Jesus Christ in restoring the "kingdom of God" on earth.

[The term "playing God" has become commonly used as a shorthand by many without religious belief to represent a tampering with the "given" order of nature, in seeking to redesign something which is fundamental to that order. There appears to be a common intuitive caution about the fundamental nature of our genetic makeup which recoils from changing it irreversibly. What is more problematic is how, in a purely secular context, one would define the order of nature to maintain that our precise genetic makeup—either as a species or a particular individual's makeup—is something that should remain inviolate.]

Having said that gene therapy could be said to be "playing God" in a right sense, and is not ruled out on intrinsic grounds, this is not to say that germline therapy is thereby justified. There are virtually insuperable ethical barriers posed by the two questions of the consent of future generations and the fact that it is hard to see how we could ever know enough about the long term effects to make a fair assessment of the risk, without actually subjecting some individuals to those same unknown risks. The only justification might be the case of some rare and utterly extreme case of a disease so serious that it could be argued that any risk could hardly be conceived as making matters worse for the individual concerned or their putative descendants. These reflections also beg the question of whether germline therapy were ever possible, in either technical or resource terms, but it is important that the ethical questions surrounding the possibility are considered.

1.6 *What should the proposed UN declaration and treaty on the protection of the human genome say?*

Response: The author of this submission represents the UK on an ecumenical working group of European churches which is currently examining the draft UNESCO convention on bioethics, and which in 1994 commented in depth on the Council of Europe's draft Bioethics Convention. Whereas the Council of Europe's convention focused too much on legal issues and not enough on bioethics as such, the UNESCO document seems to have struck a better balance, and we would commend it as a useful starting point. From this experience of interacting with these conventions, we present some of the more important points which should be included in a declaration on the human genome:

- That research into understanding the way our genome is made up and functions is to be welcomed, especially in so far as it assists our ability to combat and cure disease.
- That this knowledge is the common heritage of all humanity, and as such it should be freely available to all, and owned by all, and not the province of any Government or organisation.
- Particularly, it should be an offence to claim intellectual property rights over knowledge of any part of the human genome, or any medical practice arising from it.
- That there are some grounds for legitimate commercial protection of certain applications of genetic knowledge, but that this should take a quite different form from patenting, whose origins and concepts, derived from mechanical inventions, are inappropriate to the human person, or indeed of any life form.
- That there should be an especial effort to share the knowledge gained freely with developing countries which are unable to afford the level of research in a country like the UK.
- That commercial possibilities that arise out of human genetic research should be subject to limits. These should legislate against practices which could lead to human exploitation, and against the creation of undue monopolies or cartels.
- That non-therapeutic interventions into the human genome should be forbidden.
- That insurance companies should not have access by right to human genetic information.
- That access by employers to human genetic information of their employees should be limited to those which relate to specific, named diseases or conditions which have a direct and serious bearing

on the occupation concerned, such that the safety of the individual concerned or of others might reasonably be endangered.

— The national legislation on the human genome, genetic information and gene therapy should only be made after the widest public consultation, involving non-Government organisations and non-experts, in addition to the normal channels.

— That ethical and regulatory bodies should be required to conduct their main discussions in public, and give public reasons for the non-acceptance of any application.

2.1 *Improving Public Awareness*

Response: The aim should be to create a climate of accountability, openness and awareness on the part of scientists, government and public alike. Such initiatives as the recent UK National Consensus Conference on Plant Biotechnology should be extended to cover human genetics, and also to cover wider regions of the UK than South-east England. More effort is required, however, on the matter of responses from the Government bodies at the end of such consultative exercises at this Select Committee, the HFEA Foetal Tissue report or the DoE UK Sustainability Strategy. Having invited submissions from non-Government organisations, there is at present insufficient feedback to the participants on how issues were dealt with and why points raised by them were or were not accepted. It would very considerably help our sense of democratic participation, and indeed of the ongoing national discussion, if some rationale were given over at least the major points of debate which were raised in the submissions.

2.3 *Are there unreasonable expectations of the benefits that might come from genetics? If so how should these be tempered?*

Response: We refer you to the comments in the early sections of the Church of Scotland study group report (pp. 3-9) on the possibilities and limits of the technology. In the light of this it is clearly possible to generate a false optimism on the part of anyone involved—scientists medical staff, health authorities, Government, and especially any commercial biotechnology firms who market the drugs, diagnostics kits or other supplies. It is important to resist the temptation to oversell one's scientific discovery or therapy or product, to avoid creating unrealistic expectations by the public in general, and especially vulnerable groups who might be anxious for any sort of remedy. The role of the media in this respect is crucial. As major opinion-formers, editors of newspapers, radio and TV need to be made aware of these dangers, and so resist the temptation to make too sensational or optimistic a headline or production in the interests of "good copy", or "good TV". The role of advertising and promotional material should also be subject to careful scrutiny, and codes of practice drawn up to acknowledge the need for an especial sensitivity in this area. It is in the best interests of us all.

2.5 *What are the right questions on the bearing of genetics on human behaviour, ethics and belief?*

Response: The most important question is to ask in what context the bearing of genetics on behaviour, ethics and belief is being seen. There are dangers in taking a purely reductionist view of genetics and behaviour, a purely utilitarian view of ethics, or a purely phenomenological view of belief. Each of these presents a fragmented view, which fails to draw the connections of how each aspect fits together with the others. A Christian perspective provides such a framework for making these connections, in its holistic view of human being, as discussed in the response to 1.4 and 1.5, and in seeing human being in the context of relationship—first to God, then to our fellow human beings and to the rest of the created order.

3.2 *Are there any ethical questions about somatic cell gene therapy which are different from other types of therapy which affect only the patient receiving them?*

Response: In its report to the Government on the ethics of gene therapy, the Clothier Committee reported that although somatic gene therapy did not, in their view, represent a major departure from established medical practice, that familiar issues such as safety, unpredictable consequences and consent would assume greater importance because of the nature of genetic disorders. In that sense, therefore, gene therapy is already a special case, and so the question of "new" issues is perhaps one of semantics. The attitude to avoid is if the Clothier view were taken to mean that "there is really nothing we need to think about ethically" over gene therapy. That would be irresponsible. There is also the point that if a significant proportion of the public *perceives* there to be a difference, then, in a sense, that makes it an issue, whatever experts may think.

Although the Clothier report rightly drew attention to the continuity of medical practice and medical ethics, this does not mean we should rest on our laurels and assume that all existing medical practice is necessarily ethically acceptable. Indeed, gene therapy may throw a new light on present practices, as has happened in the cases of human genome data re the field of patenting, and of genetic information re what access insurance companies should or should not have to medical data.

With the new degree of power and specificity of treating the body at the genetic level comes also a new degree of sensitivity to error and uncertainty in a relatively young science. There are some parallels in that sense with the development of nuclear physics from conventional physics, or lasers compared with ordinary light beams. Prudence indicates a proper caution, more than simply what would be required, say, for a new drug—in

extensive and careful trials, the due consideration of side affects, in long term monitoring, and in counselling and consent procedures.

3.3 *Should information about an individual's genome be regarded as confidential?*

Response: We refer you to the significant discussion of these issues in our Church of Scotland study group's report. In respect of the insurance issue, we would draw attention to a specific point over the potential for discrimination in insurance provision against those members of the community whose genetic diseases we happen to be able to identify at this moment. It seems quite possible that, as our knowledge of the human genome matures and expands, most of the population will turn out to have genetic propensities to some condition which may be of interest to an insurance assessor. We may thus all be about as much risk as each other. In this case, to load the premium of those we know about *today*, would be immoral if, in the light of a full knowledge of our genome, they turned out not to present a much greater risk than anyone else. The Bible constantly exhorts both the people and the state to make a special point of protecting the needs of the disadvantaged in society. In this light, we would argue that those who suffer diseases like Huntington's chorea have enough suffering to cope with without the indignity of higher insurance premiums. In recognition of their suffering, they might be given preferential treatment rather than the opposite. If the rest of us had higher premiums as a result, then so be it.

4. *Economic benefits—a General Observation*

Response: It is important to keep the commercial aspect of human genetics firmly in the context of humanity. The market and profit paradigms do not readily lend themselves to consideration of the human factors of an area of commercial activity. There are many who wish to capitalise on human genetics, and there needs to be a protection of wider human interests, including the points enumerated in our response to question 3.6 (re what should be in a UN declaration), for example with regard to patenting. The trend to treat health and medicine as little more than commodities is especially to be resisted. As applications for human genetics have expanded in the USA, the temptation to treat human genetic information as something to be bought and sold has appeared to be difficult to avoid. The UK Government should take a firm ethical stance to prevent a consumer attitude to the human genome being transported across the Atlantic.

6. *Evolution—a General Observation*

Response: Following our remarks on question 1.4, we stress the importance of not seeing evolution as an isolated biological phenomenon, aside from a fully rounded view of what it is to be human. Christian teaching (and indeed common sense) shows that we are much more than just what we are as a result of genetic evolution or our current genetic makeup. This is a vitally important perspective to keep in mind when considering any of the questions on evolution in this section. All scientists interpret the meaning and significance of evolution through the spectacles of their personal world view. The theory of evolution has particularly suffered from the manipulation of those whose view of the world is reductionist, becoming used in support of their beliefs, thereby going out of the bounds of science into philosophy, but still seeking to give the impression of being "objective" and "scientific". Evolution is apt to gain a capital "E" as though it was somehow an objective personal force, and not simply a powerful model which scientists currently use to make the best sense of their data in certain disciplines. It is a subtle effect, and has long since been criticised by many philosophers of science and theologians, but it is still surprisingly prevalent.

Memorandum from Professor Sir Michael Rutter, The Medical Research Council (HGC93)
(6 January 1995)

I am responding to your letter of the 7 November asking if I would like to submit evidence for this inquiry. I much appreciate your willingness to accept evidence later than the suggested deadline of the 9 December. I am afraid that the letter came at a time when I was heavily inundated with other commitments that I could not avoid.

The questions raised by your committee are very wide ranging, and appropriately so. Because many of the questions are ones that are likely to be addressed by many other people let me focus on the issues as they apply particularly to psychiatric disorders. However, before doing so, let me make a few comments on the general issues that you mention.

The medical research community is, I think, very well aware that genetics research raises important ethical and social issues. That is particularly so because the advances in genetics have so greatly extended what is possible. It is very important that these issues are being considered in some detail by the Nuffield Bioethics Inquiry as well as by individual clinical and research groups on their own. It is important that geneticists do think about the likely consequences of their research and the great majority of them do so already. However, I

query the assumption in question 1.3 that any research will lead to "insuperable" moral problems. Certainly, some are more difficult than others but it is the job of us all to find ways of overcoming difficulties. It would be a grave error to prohibit any research topic because of the moral problems that could be presented. That is because, event the research likely to lead to moral dilemmas is also likely to lead to major benefits for society. The lesson is not to prohibit research but to think at an early stage about moral consequences and to ensure that appropriate actions are taken to avoid damaging sequelae.

Although some nongeneticists tend to think that genetics research should lead to a deterministic view of human behaviour, that is not a view that any geneticist would accept. Even single gene mendelian disorders may be susceptible to effective environmental remedies. That is so, for example, with phenylketonuria. But, in the great majority of cases, genetics plays a part in multifactorial determination, acting in a probabilistic and not in a deterministic fashion. Indeed, distinguished medical geneticists have argued that the main benefits from genetic research in medicine is that they will enable us to have a better understanding of environmental risk mechanisms. In case it may be of interest to the inquiry, I enclose a copy of a paper that I prepared for the American Institute of Medicine Committee on the Prevention of Mental Disorders. This outlines some of the range of ways in which genetic knowledge may be helpful in devising effective means of prevention. The paper was written some 18 months ago and therefore is to some extent out of date but the general points still apply.[1]

Perhaps the most public concern is expressed in relation to the genetic study of traits, such as intelligence or aggression, to which society attaches values. The worry is that there is considerable potential for abusing any knowledge that might be attained on the genes associated with such traits, and doubts as to whether such knowledge would have much value for society. These are real issues if only because the technology is now available that makes it possible to study the genes underlying continuously distributed traits of this kind. I accept that a research finding that a particular gene was associated with, say, 5 per cent of the variance between individuals in intelligence would be unlikely in itself to have much in the way of practical benefits and yet could still be open to abuse.

However, that is rather to miss the point of such research. The need is not to determine the genes underlying the normal distribution of intelligence but rather to have a better understanding of the factors, both genetic and environmental, that create a risk for mental retardation. That is because mental retardation is both associated with substantial individual suffering (such as a markedly increased risk of psychiatric disorder) and a substantial demand on services. Surprisingly, we have very little understanding of either the genetic or the environmental factors associated with the risk for mental retardation and it is very important that such knowledge be attained. One of the research issues in that connection is whether or not mental retardation is something quite different from individual differences in IQ within the normal range or whether it constitutes an extreme of normal variation. It is only as part of such an inquiry, focused on handicapping disorders, that it is of interest and relevance to determine genes involved with variations in intelligence. Broadly similar issues apply with respect to aggression. The need here is to understand better the genetic and environmental risks associated with those forms of conduct disorder that are associated with persisting social impairment that continues into adult life. Research of this kind is of vital importance, but it does have ethical consequences and it is important that these be considered now, rather than waiting for the time when some discovery will provoke the need for instant reaction. I have suggested to the Nuffield Biothics inquiry that this is an urgent priority for them to take up and my understanding is that they plan to do so. The potential benefits associated with genetic knowledge are outlined in my accompanying paper but I would be happy to give further details on any of those if the inquiry thought that it would be helpful.

Letter from Townswomen's Guilds (HGC96) (20 December 1994)

The Townswomen's Guilds is a national women's organisation with over 90,000 members throughout the UK. TG is actively involved in many issues and as you are the Chairman of the Science and Technology Select Committee, I would like to bring your attention to the Townswomen's Guilds interest in human genetic research.

At our National Council Meeting in June 1994, the following motion was carried.

"That the Townswomen's Guilds in Council assembled urges the Department of Health to monitor the implementation and outcome of all genetic screening programmes, by establishing a central co-ordinating body to review these programmes."

Townswomen are extremely concerned about developments in genetic technology and the various applications which it implies. While it is accepted that genetic screening can lead to informed choices about parenthood in certain families, there are also many harmful and distressing effects of such screening.

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[1] Not printed.

At the individual level, any involvement in genetic screening can result in acute anxiety, as certain choices have to be made, and it is agreed by geneticists that anyone undergoing screening must be counselled before and after the test.

The effects on individual rights in society could also be at risk, especially in the areas of insurance and employment. It is not hard to visualise the problems which would occur should either of these sectors have access to genetic information on individuals.

These and other concerns were also expressed at the first TG Genetics Seminar which took place on November 16th 1994 in Bristol. This event was very popular with members and produced considerable discussion. Two more Seminars are planned for Spring 1995 which illustrates just how much our members want to learn about this subject.

There is great concern about the effects of genetic screening and that research is not being properly monitored and controlled. I hope the Committee takes note of the concerns expressed by our members and that a recommendation is made to establish a body to review genetic screening programmes.

Memorandum from The Royal College of Physicians (HGC97) (10 January 1995)

BACKGROUND PAPER BY PROFESSOR J A RAEBURN FOR THE RCPE

The remit of the Committee is very wide and this may delay its report and urgently awaited responses on major issues, e.g., key questions 1, 3, 5 and 6.

The UK situation, with a network of Genetic Centres which collaborate for both service and research, provides opportunities to ensure appropriate technology transfer and feedback to families and affected patients from the clinical and scientific teams who have access to genetic expertise.

There is a clear need for extra resources and these must be made available "up front" otherwise any advantages of genetic approaches will only be realised sporadically. The purchaser/provider model for resource allocation cannot be relevant in a specialty where the purchasers do not benefit from their service provision and the benefits are not immediate.

The main recommendation of the 1st report of the Nuffield Council on Bioethics (Genetic Screening—Ethical Issues) that the Government establish central co-ordinating body "to review genetic screening programmes and monitor their implementation and outcomes" has not yet been addressed.

1. *General ethical and regulatory:*

1.3 Geneticists should, and do, think beyond immediate research goals. They should share knowledge outside the genetics community to a greater extent and be more sensitive to the views of the community and of, e.g., social scientists.

1.6 Each human being is unique. Therefore research which describes the base pair sequences of that person's DNA, whether within a disease gene or an intervening sequence, should not be susceptible to patenting and other protective measures.

2. *Public awareness and education:*

There must be more work on this, based on the few existing models for teaching genetics (in schools, antenatal clinics and in the wider community). The support of the media could be sought here (e.g., from Tom Wilkie, Science correspondent of the Independent who has written a book on genetics entitled "Perilous knowledge"). However new funding needs to be identified for increasing public awareness.

3. *Genetic disease:*

Medical genetics is a specialty where the interface between research and service provision is blurred. Traditionally services have developed in the UK from University departments which exploited their research findings in a service capacity. The speed of technology transfer depended on the total available resources. Funds

were not provided for public education, even in situations, such as antenatal screening, where the choice of the individual person or couple was essential.

3.3 If a genetic test is performed as a response to existing symptoms or signs then the result could be handled in a manner similar to any other medical investigation, including clinical examination. However, if a genetic test was performed for research purposes, or for a screening reason in an otherwise healthy individual, the clinical significance will be in doubt because there are few data to indicate the relevance to the individual, let alone to the employer or insurance company. If an individual consents to have information released, to an employer or an insurance company, then there is no problem provided the data are not interpreted inappropriately or unfairly.

3.4 The government should set a timetable for the Insurance Industry to produce *new* guidelines after full discussion with the Genetic Interest Group and other interested agencies.

4. *Economic benefits:*

4.3 Some Genetic Centres (Nottingham is an example) have developed genetic services first, prior to the development of academic elements. Such arrangements could enhance the speed of technology transfer but service units are vulnerable because they may not initially attract research funding whilst there are inadequate monies available for NHS R&D.

4.4 Yes.

5. *Research:*

5.1/5.2 Yes. Piecemeal studies may identify the structure of specific genes which cause human disease. A wider view of gene function however, will require systematic studies and knowledge of the inter-family comparisons.

6. *Evolution:*

Genetic information, and the responses of individual families to it, will influence evolution. However this is an effect of and not a reason for genetic research and service.

REFERENCES:
[1]Population Needs and Genetic Services—An Outline Guide. Published by DOH, 1993.
[2]Executive Letter EL(91)21. Purchasing Genetic Services.
[3]Report on Genetic Screening—Ethical Issues. December 1993. Nuffield Council on Bioethics.

Questionnaire on Ethical, Regulatory and Economic implications of Human Genetics Research. (Science and Technology Committee)

1. GENERAL ETHICAL AND REGULATORY

1.1 *What do we need to know . . .*

It is already known that genes are composed of DNA, that the base sequence of DNA encodes the information required to specify the amino acid sequence in the protein product and that an RNA transcript serves as an intermediate "adaptor" molecule. We have an incomplete understanding of the regulation of gene expression but overall our knowledge of gene structure and function is adequate for informed decisions to be made about the use and regulation of genetic information. Additional information—specifically as we move towards mapping of the entire human genome—will certainly accrue over the next decade or so and the relevant regulatory procedures will probably evolve, as they have done in the case of recombinant DNA experiments.

1.2 *Current policies of the MRC etc . . .*

All such bodies observe and support statutory and non-statutory recommendations with regard to the ethical and social consequences of research in human genetics. These are characterised by extreme caution and are unlikely to prove faulty in the long run.

1.3 *"Hidden agendas" . . .*

Most research topics in human genetics would be regarded by "society" as rather mundane. There is no hidden agenda to create a "super-race". Fiction is more imaginative than science in this regard. Most scientists, including geneticists, find "the art of the possible" quite exciting enough without feeling the need to indulge in fantasies.

1.4 *Determinism and improving the world . . .*

The goal of geneticists is to understand the world rather than to change it on any large scale. One intriguing aspect of genetics is the way in which environmental factors interact with genetic ones. This implies the opposite of determinism. The world may be improved to some small extent by prevention or successful management of specific genetic disorders. There is no moral difference between doing this and treating infectious, traumatic or other types of disease.

1.5 *Germ-line therapy . . .*

I do not believe there should be any ethical objection to eliminating—say—the gene for sickle cell disease or for any other specific genetic disorder in the germ-line if we could be certain that no untoward perturbation of the DNA would ensue. It seems highly probable that germ-line therapy of this type will become feasible and safe in the foreseeable future. The major effect will be to reduce the burden of treatment for individual mutation carriers. N.B. Where a dominantly expressed mutation is corrected in the germ-line it will have only a limited effect on the population frequency of the disorder since many cases arise through new mutations.

1.6 *UN treaty on protection of the human genome . . .*

Manipulation of the genome—somatic or germ-line—should be done only to correct specific identifiable deleterious mutations, not to enhance "desirable" normal traits. It should be undertaken only with informed consent of the subject (or of the parent or guardian, as appropriate for those unable to give informed consent on their own behalf).

2. Public awareness and education

2.1 *Public knowledge of genetics . . .*

As with most branches of science, public knowledge ranges from the abysmal to the admirable. In the case of genetics, misconceptions abound and are fuelled by science fiction, not always advertised as such. Members of families affected by genetic disorders are often very well informed and do excellent work in educating others. Organisations such as the Genetics Interest Group (GIG) might be encouraged to play a greater role in public education but unless more is done to promote the teaching of basic science in schools, it may prove impossible to raise the general level of understanding of genetics to an acceptable level.

2.2 *General suspicion of genetics . . .*

Yes. See 1.3 and 2.1 above.

2.3 *Unreasonable expectations . . .*

It may be widely believed that cures will eventually be found for genetic disorders but this is not necessarily unrealistic. The key question is the timescale. No doubt some people imagine that discovery of a gene if virtually equivalent to curing the corresponding disease but many others (in my experience) are hoping for some benefit to accrue to the next generation which may not be unreasonable. As more and more practical examples can be cited of the hurdles to be overcome before mapping can be translated into therapy, public expectations will probably be tempered. Cystic fibrosis is a case in point. Most people know a little about this condition and the progress of gene therapy trials has received fairly accurate publicity.

2.4 *Genetics and socially unacceptable behaviour . . .*

Almost anything—(PMT, lead poisoning, a deprived childhood, television) can be, and has been, used as an excuse for socially unacceptable behaviour. There is no reason to suppose that genetics will be any different. Similarly, it could conceivably be used to justify changes in social policy with no more or less validity than many other arguments for such change.

2.5 *Questions on the bearing of genetics on human behaviour, ethics and beliefs . . .*

At this stage the only manageable questions that can be addressed in man relate to extreme disorders of behaviour, such as overt psychopathy. It may indeed be important to understand the role (if any) of major genes in these pathological states. As regards more general considerations such as genetic contributions to continuous variables like aggressiveness/passivity, animal studies are more appropriate.

3. Genetic disease

3.1 *Research versus service in genetics . . .*

This is a major and universal problem. As the question implies, there should be a smooth transition from research to service both in terms of how genetic work is organised and of how it is financed. In fact, as the research impinges on patient care, it becomes a funding nightmare. Demand for services increases as advances in the basic sciences are recognised. The research community (e.g., MRC) becomes worried about the potential costs of supporting a clinical workload while the NHS finds itself unable to provide funds for a "new" service, particularly one that has yet to prove itself cost-effective in terms of disease prevention or effective treatment. Hence, just when basic research becomes most relevant clinically, it becomes most precarious financially.

This is particularly serious in genetics which, by its nature, is long term work (measured often in human generations rather than months or even years). Research-based clinics run the very real risk of collapsing, through lack of funds, after being supported by committed members of families affected by genetic disorders for many years. Communication between, for example, the MRC and the NHS is abysmal despite publicity given to the "concordat".

Some genetic disorders are probably not studied at all because they do not affect sufficient individuals to justify investment by the NHS and because they do not have a convenient animal model (which would excite the MRC in a way that human patients do not). My own experience, however is in familial forms of common cancers which have a very high incidence relative to most genetic disorders and which suffer from the frightening scale of demand for diagnostic and counselling services.

3.2 *Ethics of somatic cell gene therapy . . .*

The issues are very similar to those that arise in relation to any other kind of therapeutic trial.

3.3 *Confidentiality . . .*

This can be argued both ways. The big problem at present is that only a few deleterious mutations can be identified so that a major element of "unfairness" enters into the equation. Those who happen to carry "bad" genes that can be detected now will suffer discrimination relative to those whose equally harmful mutations may not be uncovered for another twenty years. Eventually some *modus vivendi* will need to be worked out with insurance companies, employers and the like.

3.4 *Population screening . . .*

For relatively common treatable conditions, population screening should be encouraged. There is obviously an economic trade-off to be made between frequency of the disorder, treatability and cost of failure to diagnose early. Thus it can be argued that population screening for phenylketonuria is justified despite its rarity. Guthrie test cards have much to recommend them for genetic diagnosis. There is unlikely to be substantial public resistance to sensible programmes but an opt-out clause might be incorporated into any scheme to preserve its voluntary status. Counselling services may be severely strained if population screening for potentially serious recessive disorders (e.g., cystic fibrosis) is introduced on a wide scale since the options that arise in that situation include voluntary childlessness and selective abortion.

3.5 *Protection from discrimination . . .*

See 3.3. above. If screening is introduced and encouraged partly to reduce the healthcare and social costs of genetic disorders then it will be in "society's" interest to ensure that potential carriers of deleterious mutations are not inhibited from participating in screening programmes by fear of adverse employment or insurance prospects.

3.6 *Preconception exchange of genetic information . . .*

As things stand at present, there are only a few situations where this is likely to be a serious proposition:- Cystic fibrosis in the "Western" world, haemoglobinopathies in tropical Africa and Cyprus and recessive disorders in certain inbred communities. In such settings, sharing of relevant genetic information by partners

before conception is already accepted practice and this is likely to increase (though perhaps not enormously) with developments in genetic research.

4. Economic benefits

4.1 *Value of genetic knowledge for disease management . . .*

Quite apart from the (probably limited) place of gene therapy, knowledge of the precise genetic basis of disease is likely to lead to major advances in drug design and other approaches to treatment. The process has scarcely begun and may not have a major clinical impact for many years; however it represents the change from empirical to rational management of disease and hence its significance can hardly be exaggerated.

4.2 *Differences between gene and conventional therapy . . .*

Gene therapy is a rather blunt instrument with a limited place in the therapeutic armamentarium. That place has still to be defined but will probably be confined to a very few disorders where no more effective alternative has been developed: development and treatment costs may be rather similar for gene therapy and for drugs designed through the application of genetic knowledge.

4.3 *Factors influencing commercial exploitation of genetic research . . .*

I do not have sufficient knowledge of—or interest in—these issues to make any sensible comment and I suspect many research workers are in a similar position. There is usually such a lag between discovery and exploitation that little thought is given to the question of commercial factors until far too late (at least in the UK).

4.4 *Regulations in the UK and elsewhere . . .*

As far as I know, the regulatory regimes in the USA and other developed countries are broadly similar. What differs very markedly is the relative availability of research funds, both venture capital and governmental. The fiscal and political climate in the USA is much more conducive to liberation of money for medical research because venture capital is essentially tax-deductible and because pressure groups (e.g., on behalf of those with particular diseases) wield much greater political influence. This may not always be a wise or a good thing but, in the long run, if knowledge is power and especially if patentable knowledge is commercial power, we shall see an ever greater imbalance between the USA and the rest of the world in terms of access to advanced medicine.

4.5 *Non-medical by-products of human genetic research . . .*

It is hard to envisage any—perhaps serendipity will play its part but in strictly genetic terms there is little difference between man and lower species. Therefore advances that are not directly related to human genetic problems are more likely to emerge from basic genetic studies in simpler experimental systems that from clinically orientated research.

5. Research

5.1 *Mapping the human genome . . .*

Ultimately, mastery of human genetics requires knowledge of the complete human gene map. Whether that should be a high priority *now* is debateable. Mapping expressed sequences only is a form of "short cut" which is technically amenable to a high degree of automation and may lead to some commercially exploitable findings. It is not a substitute for mapping the complete genome, merely one route to that objective.

5.2 *Systematic versus piecemeal studies of the genome . . .*

In theory, at least, the whole human genome could—and would—be mapped through piecemeal studies. One major advantage of a systematic approach is the gain of efficiency through organised multi-centre co-operation which should minimise wasteful duplication of effort. That, in turn, is attractive to potential funding agencies, including governments who anticipate good value for money and are fearful of missing out on some (admittedly rather nebulous) "pay-off". Thus it may be argued that the human genome project, like massively expensive collaborative programmes in other areas of science, is funded while more original, possibly more worthwhile (and even more profitable) small-scale projects lose out.

5.3 *Nature versus nurture . . .*

How long is a piece of string?

5.4 *Organisation of coding information . . .*

Good question. Surprises, such as the extent of "functional clustering" of related genes, or the "nesting" of one gene within another, turn up all the time. The possibility of unforeseen effects of supposedly precise manipulation of the human genome is a real one and is very well recognised by those who contemplate gene therapy as well as by the regulatory authorities.

5.5 *Financial support . . .*

Any genetic researcher must admit to a bias in answering "no". We still do not know the true scale of the genetic contribution to human disease. Its major place is probably in the common multifactorial disorders like atheroma and cancer but genetics is still equated in the public mind largely with rare conditions. Hence there is a false perception (underestimate) of the potential of advances in genetics to impinge on human health. This is probably reflected in the level of funding for research as well as in the plans for genetic services in the NHS.

6. Evolution

6.1 *Continuing evolution in man . . .*

There is no reason to doubt that evolution is continuing but the rate of evolutionary change would be much too slow to measure in real time.

6.2 *Social organisation and human evolution . . .*

On the evolutionary time-scale, "modern" is almost a meaningless term. Social change would probably have to be established for many thousands of years to have even the slightest impact on natural selection of human genetic characteristics. Mixing of ethnically (hence genetically) different strains within the species has become more pronounced during the 20th century but it is doubtful whether this has had any profound effect on the genetic characteristics of man. In health terms, it tends to reduce the incidence of serious recessive conditions by reducing inbreeding.

6.3 *Human evolution and environmental change . . .*

See 6.2.

6.4 *Scientific knowledge and evolution*

Impossible to predict but developing scientific knowledge has always been a component of evolution and is bound to remain so. The world has never been a static environment. It would be inappropriate to expect it to become one now.

6.5 *Evolutionary impact of selective fertilisation etc . . .*

Probably negligible. The rate of new mutations will probably always exceed any effect of human intervention.

6.6 *Clinical intervention versus natural selection . . .*

Essentially they involve the same process. The only difference is that alteration of the genome in the clinical setting is directed and controlled. Long-term stability—or otherwise—of the induced genetic change will depend on the same background mutation rate and selective pressures as any other genetic attribute.

6.7 *Interference with the process of evolution . . .*

See 6.2 and 6.5.

Memorandum from the Medical Research Council (HGC98) (January 1995)

1. General ethical and regulatory

1.1 *What do we need to know about the ways in which genes work in order to make decisions about the use or regulation of genetic information? Are we like to obtain that information?*

It will be important to know whether a genetic disease is dominant or recessive and whether it is sex linked before we can begin to use the information for counselling. It will also be important to know whether particular sequences are becoming unstable, how often sequences become mutagenised, and how often mutagenesis leads to new targets. There is much information available already from animal experiments (e.g., on the fruit fly *Drosophila*) but more data are required; such needs can only be satisfied through further research.

The exact use to which human genetic information is put is very important, For example, we must be very sure that DNA fingerprinting is reliable when used for convictions or for paternity suits; reproductive choice, on the other hand, may only need a probability range for the chance of bearing an affected offspring. Conventional considerations, such as false positive and false negative are also important, as is variation in the severity of disease, and the population base used for probability (e.g., in the context of fingerprinting). In terms of gene therapy there are many other considerations (e.g., the targets cells, regulation of gene expression etc.).

Human genetic information has already found a number of successful applications; for example, genetic fingerprinting and virtual eradication of thalassaemia from the Cypriot population via screening programmes.

Valuable lessons may be learned from experiences with AIDS about the ways to handle information in relation to insurance etc.

1.2 *Are the current policies being pursued by the MRC and other research funding bodies with regard to ethical and social consequences of research in human genetics adequate?*

MRC invited the DH and the relevant regulatory authorities to nominate representatives as full members of its human genetics committees to ensure that current policies meet with regulatory guide-lines. Thus, representatives of the DH, SoHHD, GTAC, MCA and NIBSC attend the Gene Therapy Co-ordinating Committee, representatives of the DH and the SoHHD attend the Genetic Approach the Human Health Steering Committee and the DH preferred to receive papers from the HGMP Co-ordinating Committee rather than to attend the meetings. MRC Boards, the Strategy Committee and Council include representatives of the DH and SoHHD; the Departments receive the papers for all MRC Grants Committee meetings. The MRC Gene Therapy Steering Committee additionally includes amongst its membership ethicists and psychosocial/behavioural experts.

1.3 *Has society a right to declare that some research topics should be prohibited because they are intrinsically likely to lead to insuperable moral problems? Should geneticists think more widely than their immediate research goals and their likely consequences or should they leave that to others? Are they pursuing hidden agendas of which the public is unaware?*

Provided appropriate regulatory bodies are in place and include lay membership, then the question of society declaring that some research topics should be prohibited should logically not arise (e.g., even though IVF using embryos from fetal eggs is not acceptable, basic research using fetal eggs should continue; it may for example, lead to the knowledge needed to remove eggs from cancer patients undergoing whole body therapy, so that they can be preserved, matured and thereby permit subsequent fertilisation and replacement in the mother). Debate should be encouraged to ensure that society has a voice in the formulation of laws. Initial fears are often allayed as new knowledge is accumulated and disseminated.

Human geneticists are unlikely to forget the wider implications of their research particularly in the light of the problems of eugenics.

Human geneticists are primarily interested in taking forward knowledge with a view to developing new therapies or technologies. Research funding is not awarded lightly and approval by the appropriate regulatory authorities is always demanded where relevant.

1.4 *Does research into human genetics lead to a deterministic or any other particular view of human behaviour? Will people try to improve the world through genetic interventions? Should they?*

Human genetics differs from most biology in that information gained about an individual has implications for their family; hence conventional ethical concepts relating to the individual need to be modulated. MRC recognises and funds important research on environmental effects. Most geneticists are acutely aware that genes only act in an environmental context, never in isolation. There is no evidence currently of crude determinism; vigilance and efforts to increasé public understanding should go hand in hand with genetics research.

Geneticists, like scientists working on other approaches, are trying to improve knowledge, advance technology, improve agricultural stocks and strains and design new therapies. These will all lead to beneficial improvements of one kind or another, statutory laws and regulations mitigate against harmful outcomes.

1.5 *Germ line intervention would affect later generations who cannot give their assent. Are there other objections in principle to it which go beyond our limited knowledge of what those effect might be? Would this be playing God? What does this mean and why would it be wrong?*

All reproductive choices affect later generations. Germ line gene therapy would affect the gene pool which is the source of human genetic variability. Little is known about the possible consequences and any harm to future generations would take a long time to discover and deal with. However, there is a considerable volume of research on animals and plants which is illuminating the general consequences of germ line manipulations. Patient groups, particularly those associated with recessive disorders, where there are carriers (e.g., CF), are beginning to question why germ line gene therapy is illegal, since in such cases somatic gene therapy will not address the carrier status.

1.6 *What should the proposed UN declaration and treaty on the protection of the human genome say?*

The MRC is aware of the discussions in the UNESCO Bioethics Committee and is in regular contact with the UK member, Mr David Shapiro of the Nuffield Council on Bioethics, providing him with scientific advice when appropriate. We have also discussed progress of the Committee with the Chairperson, Mme Noëlle Lenoir.

The MRC's concern is to ensure that the Committee is soundly advised on the science underlying the ethical issues under debate. We are therefore pleased to see that Mr Shapiro is acting as rapporteur for the working group on genetic screening and testing and that Professor Peter Lachmann (Director of the MRC Molecular Immunopathology Unit) is a member of the working group on gene therapy.

The MRC is not in a position to comment on the scope or overall content of the Declaration or its likely future.

2. Public awareness and education

2.1 *What is the extent of knowledge of and interest in genetics among different sectors of the public? Should steps be made to improve this and, if so, what form should they take?*

Broad public participation will be required to develop educational approaches that respect the widely varying personal and cultural perspectives on issues of genetics and are tolerant and respectful of individuals with genetic disorders of all kinds. Knowledge and interest in genetics amongst the public should be encouraged through the media, through schools liaison, open days and science festivals. Scientists, doctors, clinicians and the media have important roles in formal and informal public education.

The White Paper "Realising our potential" gave MRC, and other Research Councils, a formal responsibility to develop public understanding of science. The MRC campaign will focus on MRC scientists themselves taking responsibility for ensuring that the public has some awareness and understanding of their work. Plans include working with schools, taking a more active role at science fairs, joint activities with the Women's Institute and training for teachers in the latest scientific findings. Genetics will inevitably have a high profile in this campaign. The "MRC News" has been reformulated to include articles on research of topical importance written by scientists from MRC Units and from HEIs; it is now distributed to GPs surgeries and to schools.

2.2 *Is there general anxiety and suspicion about research in genetics? Is it justified or should it be allayed and, if so, how?*

The most recent EC survey conducted last year indicated that there is general optimism that new technologies will make life better. Those who know most about science were most optimistic about genetic engineering. This suggests that providing more information will foster more positive attitudes. Over 90 per cent of the Europeans wished to see some controls in place. A recent UK poll of public opinion published in the Daily Telegraph suggested that only a tiny minority of the population are against gene therapy aimed at improving human health.

There is currently much interest in the general public about genetics. However optimism about potential health benefits of understanding the nature and function of human genes is tempered by concerns about the potential applications. Some of these may be groundless but many stem from knowledge of eugenics. In the UK these concerns have been addressed by the development of ethical guide-lines for clinical practice; these include the Nuffield Council on Bioethics recent report on genetic screening and the Clothier report on the ethics of gene therapy. All these guide-lines emphasise the importance of giving patients good information. The second approach is to conduct research to see how best to implement genetic developments.

2.3 *Are there unreasonable expectations of the benefits that might come from genetics? If so, should these be tempered?*

There are possibly some unreasonable expectations of the benefits that might come from genetics in terms of time. Once a gene responsible for a disease is identified, the public often conceive that a cure is imminent. Unreasonable expectations would be tempered by the provision of comprehensible, accurate information to the public.

2.4 *Is there a danger that genetics will be seen as an excuse for socially unacceptable behaviour? Could it be used to justify reductions in social programmes of health education and welfare?*

Environmental factors will impact on every genetic disease therefore it would be inappropriate to use genetics as an excuse for socially unacceptable behaviour. This will however, require better public understanding and awareness. For the same reasons reductions in social programmes of health, education and welfare could not be justified.

2.5 *What are the right questions on the bearing of genetics on human behaviour, ethics and belief?*

Research aimed at defining the questions that need to be asked of patients in relation to genetic disease falls squarely within the remit of the MRC Genetic Approach to Human Health Initiative; a call for research proposals in this area was recently issued.

3. GENETIC DISEASE

3.1 *How much of genetic diagnosis is conducted as a routine medical service and how much is associated with research programmes? Is the continuity between the two sufficiently well organised? Are some diseases with a known genetic cause not being diagnosed and, if so, why not?*

Most diagnoses are probably conducted in a service manner, but are certainly not routine; pilot projects might, on the other hand, be considered as research. Scientific endeavour centres on the development of new or improved diagnostic tests.

Demand from families is an important factor in terms of which diseases are being diagnosed; the existence of an effective lay society also raises the profile of a disease. On the other hand, the development of diagnostic tests for diseases where treatments are of limited effectiveness, or where no treatments are currently available is unsatisfactory.

Education and counselling are vital components of the genetic testing process; MRC funds research into these important issues.

3.2 *Are there any ethical questions about somatic cell gene therapy which are different from other types of therapy which affect only the patient receiving them?*

The Clothier Committee concluded that somatic gene therapy raises no new ethical questions. Their view was that we should apply existing ethical codes, and the principles on which they are founded, to gene therapy (it is analogous to transplantation).

3.3 *Should information about an individual's genome be regarded as confidential or should it be possible for employers, insurance companies etc., to require genetic tests or to obtain the results of previous tests on an individual or their relatives? If not, why is genetic testing any different from current medical tests?*

Public knowledge about a patients predisposition to genetic disease may lead to stigmatisation or discrimination and exclude him/her from arranging insurance or gaining employment. The rights of individuals must be considered in these contexts. The development of powerful new diagnostic approaches will expand the repertoire of tests available; viewed from the correct perspective this is an advance rather than a new source of problems. The distinction between health insurance and life insurance may help resolve these issues, but legislation will almost certainly be required. Leads could be taken from experiences gained in the AIDS field. Everyone has long known that all sorts of conditions run in families. Life insurers currently ask about the cause of relatives' deaths and there are already many conventional tests of "at risk" status e.g., blood pressure.

3.4 *When is population screening for genetic disease appropriate? What factors, such as costs and the availability of counselling and treatment, should be taken into account? How should screening be organised and regulated?*

Population screening would have to take into account disease burden, incidence/prevalence, cost/benefits, availability of implementation services including counselling etc. Also whether there is an effective therapy for the disease being screened for. The Nuffield Report recommends that the DH should set up a central co-ordinating body to review genetic screening programmes and to monitor their implementation and outcome.

3.5 *If screening for a wide range of genetic predispositions becomes routine, how will people be protected from discrimination on the grounds of their genotype? Should they be?*

It is not appropriate for the MRC to express a view on these questions.

3.6 *Would people be well advised to seek genetic information from sexual partners before the conception of children? Are they likely to? Is this likely to change with future research?*

It is not appropriate for the MRC to express a view on these questions.

4. Economic benefits

4.1 *What assistance in the treatment of disease or the design of drugs is given by knowledge of the gene(s) associated with a particular disease?*

Any knowledge about the localisation, structure and function of genes will facilitate the development of treatments or rational drug design whether they be genetic or chemotherapeutic.

4.2 *Are there differences in principle or in practice between gene therapy and conventional therapy? How might these affect development costs? How will this affect the actual costs of treatment?*

Thus far, gene therapy is focused on corrective treatment, as opposed to other therapies which may be corrective or preventative; however, one might envisage gene therapy being developed for high risk genes.

The development costs of gene therapy, like any new therapy, will be expensive, particularly the setting up of trials. The costs of treatment via gene therapy are unknown at present.

4.3 *To what extent do factors such as technology transfer facilities, patent protection and regulation, influence the commercial exploitation of research findings?*

Many countries accept the value of a patent system in encouraging innovation and promoting the development of new products and processes. the recent GATT agreement extends this support to the Patent system across the globe.

Patent protection is particularly important in the biotechnology and pharmaceutical fields, since without the (temporary) monopoly or exclusive position offered by patent protection, the cost of research, development and clinical trials could be prohibitive (i.e., without the prospect of an exclusive position, a company could not make the massive financial investment required).

Technology transfer facilities assist science base/academic groups in identifying and protecting intellectual property, in licensing or assigning rights to industry or engaging in research collaborations with industry and transmitting "know how". These abilities are crucial to commercial exploitation.

4.4 *How does the regulatory regime for genetic based industry in the UK compare with that in other countries? Is there a danger that investment will be lost to other countries with different regulations or with better venture capital funding potential?*

There are some indications that restrictive regulations will inhibit investment in the country concerned (e.g., Germany). Multinational pharmaceutical companies can divert research investment to less restrictive countries. It is generally believed that the UK regulations are currently more favourable to early clinical testing of potential biological therapeutics than many other competitive countries, including the USA.

The ability to raise funds through the venture capital route for the launch and progression of "start-up" biotechnology companies is a key factor, and possibly a more important factor that the precise level of regulation. Despite public quotation of companies, and therefore an earlier exit route for venture capital, there still remains a wide disparity between the US and UK in their ability to raise capital for biotechnology. We believe the climate in the UK could change rapidly if the first biotech companies "floated" prove successful. However, within the UK there is a shortage of personnel with the necessary blend of entrepreneurial skill and commercial and technical understanding to act as Chief or Senior Executive in boitech start-up companies.

The MRC has set up an Industrial Advisory Group, comprising top managers from several major UK pharmaceutical companies, to provide advice on exploitation of the data generated by the genome project and gene therapy.

4.5 *What products, other than medical diagnostics and therapies, might be produced as a result of genetic research?*

As a result of genetic research, improved strains of plants and animals (e.g., leaner meat, increased milk yields, yeasts for brewing) will be generated. Species will be developed which are suited to particular environments (e.g., drought resistance). New hardware, software, networks, robotics, database management and information retrieval systems will be developed that have far reaching applications beyond genetics and disease.

5. Research

5.1 *Why is it worthwhile to map and sequence the human genome? What are the advantages of mapping expressed genes only versus completely sequencing the genome?*

The human genome consists of some 3 billion bases on 24 distinct chromosomes; it is believed these compose some 50-100 thousand genes. The aim of the human genome programme is to locate the position of all of the DNA and to decode the genetic information contained therein. This will of course include aberrant information present in disease genes. Strategies centre on construction of the genetic map, the physical map and ultimately

the complete DNA sequence. The genetic map shows the relative positions of gene loci on the chromosomes and is derived from studies of inheritance. The physical map shows the identifiable landmarks (e.g., genes or markers) on DNA regardless of inheritance. Sequencing is the ordering of nucleotides in a stretch of DNA, a gene, a chromosome, or the entire genome.

Sequencing of the whole genome will reveal sequences with important functions that might otherwise go unidentified. Since only around 10 per cent of the bases are thought to contain useful information, some researchers have opted to sequence only the expressed genes; this approach offers short term returns by avoiding gene poor regions, however, it has a number of inherent problems. Firstly, it is probably impossible to discover all of the genes; secondly, the possibility of studying control sequences is denied; thirdly, complete sequences are not always easy to obtain for large genes; fourthly, sequencing costs will fall only in the context of large scale genomic sequencing, and lastly there are problems in dealing with multigene families.

The MRC supports work using both strategies.

5.2 *What will it tell us about the human species and the individual that would not otherwise accrue from piecemeal studies?*

The human genome project is a task too great for any one country to succeed alone. One of the special features of genome research is the requirement for national and international collaboration. Different research groups work on specific levels of genome organisation. Co-ordination of these approaches can be further enhanced by combining the efforts of groups with specific technical expertise, so as to generate more multi-disciplinary approaches. Further as information emerges about the sequence and function of various genes, it must be assembled into a single up-to-the-minute picture which is available to all researchers. All this systematic effort will provide a complete understanding of the genetic basis of man. Piecemeal studies would not benefit from the co-ordinated approach that permits the significance of newly generated information to be appreciated in the broader context.

5.3 *To what extent are human characteristics determined by the genome and to what extent does the environment influence the expression of genes?*

Normal variations in human characteristics such as personality, intelligence and physique may be explained by the inheritance of multiple genes and their interaction together with environmental influences. Such genes do not determine personality or behaviour—there is little doubt that the social and psychological environments that envelop a child in his/her formative years are the most powerful influences in personality and future behaviour—but the genes can influence how a child reacts to its environment.

5.4 *How much is understood about the organisation of coding information in the genome? Is it conceivable that interventions such as those produced by gene therapy might have unforeseen effects?*

The human genome contains up to 3 billion base pairs, but it is believed that only 10 per cent of these may contain useful information which is read out in blocks called exons; the exons are separated by DNA segments called introns whose function is presently unknown.

The aim of gene therapy is to make good defective genes in the body cells where it is required, by providing the right genetic information, under proper control, in precisely those cells that need it for their normal function. Thus far it has only been possible to supplement a defective gene, not to replace it, neither is it yet possible to lodge a gene precisely where it would naturally be. In time it may be feasible to harness the natural process of recombination which allows formation of new combinations of genes. Much new information is being accrued through the use of animal experimentation. Legislation is in place to ensure that procedures are conducted at the highest practicable safety levels (e.g., Clothier Report and the Gene Therapy Advisory Committee).

5.5 *Is the financial support for research in human genetics adequate when compared with the results which may flow from it?*

Additional support would facilitate a faster and more extensive outcome. Although some costs (e.g., for sequencing or diagnostic tests) will probably fall as technologies are improved. If the UK is to exploit traditional strengths and remain a major player on the international scene a greater level of support is needed.

6. Evolution

6.1 *What evidence is there for continuing evolutionary change in humans?*

Evolution can simply mean biological evolution, or the total evolution now dominated by social interactions.

There is extensive evidence of continuing evolutionary change in humans. For example, the new world was populated some 25,000 years ago, but changes in the skin colour of populations of Central South America and the tip of South America have been recorded in the last 10,000 years.

6.2 *What may be the consequences of modern social organisation for human evolution?*

Modern social organisations is crucial to the future of human evolution. Human are no longer a rare species and there are no longer the same opportunities for genetic drift. For example, tribal people in the Amazon living in different villages were genetically very distinct 1,000 years ago; this is no longer the case.

6.3 *What may the consequences of environmental change be for human evolution?*

The consequences of environmental change for human evolution are less than one might think. People are now able to manipulate the environment to suit themselves so there are no longer the same pressures for human evolution. For example, in the case of diabetes, or PKU, diets have been actively changed rather than simply leaving change to human evolution.

6.4 *What may be the consequences of the pursuit of scientific knowledge for human evolution?*

Pursuit of scientific knowledge may alter human evolution indirectly (e.g., curing sickle cell disease, which protects against malaria, might force evolutionary change to compensate).

6.5 *What might be the evolutionary impact of selective fertilisation or termination and of other forms of extreme discrimination?*

Such effects are somewhat unpredictable. In the case of rare, persistent, harmful, dominant diseases (e.g., Huntington's chorea) selective fertilisation or termination is possible, but the scale on which this happens has low impact. For recessive disorders the impact is more unpredictable due to the effect of reproductive compensation (i.e., couples tend to have additional children to compensate for any lost through selective termination).

6.6 *In what ways does manipulation of the germ line in the clinic or laboratory differ from natural variation?*

The first question is well covered by the Clothier Report. Somatic gene therapy is essentially equivalent to transplantation. There is a need for safety considerations and the source of the gene may worry some people. Germ line gene therapy is potentially a better solution, but since it affects the next generation there is a greater obligation for safety. However, this is also true for many conventional treatments (e.g., cytotoxic drugs for cancer patients). The situation vis a vis germ line gene therapy needs to be reviewed in due course in the light of experiences with somatic gene therapy.

Natural variation involves three processes:

(i) There is one chromosome pair in each parent. At random the progeny will inherit from each parent, one of the two chromosomes in each pair.

(ii) Rare recombination events leading to new combinations of DNA on one chromosome.

(iii) Rarer mutations leading to a modified gene.

Laboratory manipulation can involve all of these, but typically specifically seeks to focus on recombination in insert the normal form of the disease gene. In the laboratory it is possible to introduce genes from different species not limited by conventional hybrid non viability/sterility.

Experimental manipulation of the germ line which introduces mutations in a non targeted and small scale way will not be different from mutations that occur through natural variation. Significant effects on the germ line would only be generated by large scale manipulations (e.g., those involving all patients and carriers of a particular genetic disease world-wide). However, natural variation is an ongoing process and it is often the case that as soon as one disease is eradicated from the global population it is replaced by another (e.g., polio and AIDS).

Trials of gene therapy in patients are just beginning. Success will depend in part upon acceptability both to the public and to those eligible for trials. This in turn will depend on the quality of the information provided both in the public arena and in the clinical setting.

MRC is committed to increasing public understanding of scientific developments in all fields of research.

6.7 *Human evolution has been by sexual reproduction guided by human behavioural drives. Should clinical interventions be allowed to interfere with this process?*

When people choose partners they usually do so with great care; however, individuals diagnosed as being carriers of or susceptible to harmful genetic disease may find it more difficult to forge partnerships. The choice as to whether diagnosis takes place must be on the basis of informed consent. The disease is managed by ensuring that the individual is provided with all necessary information.

Clinical interventions have long interfered with this process. Quite apart from treating infertility and preventing unwanted pregnancies, clinical interventions have allowed people with certain genetic diseases to survive and reproduce, hence influencing the gene pool.

Memorandum from Dr T Harris, Vice President of Sequana Therapeutics Inc., (HGC101)
(16 January 1995)

Thank you for your letter of 19 December. I have done my best to answer the questions but some of them were out of my frame of reference. I hope they are useful anyway.

I would be very pleased if the committee could find some time to visit Sequana since we are proud of what we have achieved.

One of the reasons I extend this invitation is because there is probably nothing here that could not have been done in the UK given the right circumstances, particularly the attitude of funding agencies and access to venture capital. There is a lot of expertise in the UK. It is a veritable mecca for molecular genetics (half of our scientific advisory board is actually working in the UK!) and we have several UK trained people working here.

As I have said in public in the UK before (some would say *ad nauseam*), I think it is very important for us to be able to compete with the USA in the field of high technology biological ventures. We have some of the world's best pharmaceutical companies based in the UK and we need to retain them there. Given the state of the pharmaceutical market place they are going to need to outsource some of there R&D. This should be to small bio-companies in the UK (if there were any!) rather than in the USA. I would like the committee to get some idea first hand of the look and feel of a venture capital backed start-up. I have expanded on this theme a bit in the attached as you specifically asked me to in your letter. If nothing else this serves to put the record straight.

Why Sequana?

In early 1993 I became aware of the fact that new genetic mapping technology would make it possible to uncover those genes that were involved in controlling predisposition to common diseases such as diabetes and asthma. This information will be of supreme importance to pharmaceutical companies (who have currently too many targets to explore) because it will provide a *genetic* validation for working on a particular molecular target.

I managed to persuade Glaxo (for whom I then worked) that they should get involved. This resulted in the Glaxo Genetics Initiative—an in house programme in Genomics research. I also explored the possibility with several UK venture capital firms of starting a company in this area.[1] The concept was very much like what Sequana has turned out to be. The venture capitalists were worried primarily about short term return on investment and exit route. More importantly though, the funding agency most involved in supporting work in this area (The Wellcome Trust) was completely unable to deal with the fact that some of the work they were supporting might have commercial value. This made it almost impossible to go forward because they had no mechanism for licensing technology nor any expertise whatever in the commercial arena. Their naiveté was a revelation. The MRC, in contrast, was helpful but did not command much of the technology that was needed.

The Wellcome Trust have now formed an arrangement with CRC technology (Dr Sue Foden) which, had it been in place two years ago, might have helped to sort things out. In the end, the time it was taking to go from first base (eight months with no progress) told me that it was never going to happen in the UK (and it still hasn't). Kevin Kinsella, an archetypal (read real) venture capitalist in San Diego had already set up Sequana Therapeutics, and he asked me basically to put my money where my mouth was (and be VP R&D). As I usually do what I say, here I am with my wife and family in sunny Southern California.

Would I rather be doing this in the UK?

The answer is "if I could I would" . . . despite the rain.

ANSWERS TO UK QUESTIONS

1. *General ethical and regulatory*

1.1 The same mutation in the same gene (whether controlling levels of protein expressed or function of the expressed protein) can lead to different phenotypes depending on the genetic background of the individual. This information will become available but it can make counselling difficult, i.e., the severity of a disease cannot be predicted from looking at a single gene even in monogenic disorders.

1.2 At present they are sufficient.

1.3 Everybody is entitled to enter the debate. It is not one for geneticists alone. Generally scientists are only too well aware of what could go wrong and are not irresponsible. Nevertheless, in fields like germ line gene

[1] NB Sequana is a Genomics company not a Gene Therapy company (see attached).

therapy, they have to be able to persuade others that what they are doing is safe before doing it. For example, the data from model systems has to be there.

1.4 Not really. Natural selection is a stochastic process. We are at the stage where we can even conceive of what we might do to improve people genetically but do not know how to do it. I am sure that if safe procedures for genetic improvement were to be available then they would be used.

1.5 I think there are issues here which go further than just the science. However the opinions are ones of personal believe rather than ethics in my view. The debates should be had.

1.6 No comment

2. *Public awareness and education*

2.1 Generally, this is awful. The population at large is extraordinarily ignorant about science in general and genetics in particular.

2.2 Yes, there is and it is not wholly unjustified either. The Tabloid Press with their consistent "mad boffins" view of science (TV too) do nothing to help. In fact, they always make the situation worse. Good objective reporting of science would help a lot. The US newspapers (e.g., the New York Times) do a much better job and enter into *informed* debate.

2.3 Not at the moment.

2.4 Possibly: there have already been examples, e.g., the family with monoamine oxidase mutations leading to violent behaviour. Having genetic predisposition to any behavioural trait is not an excuse for antisocial behaviour, but it could be part of an explanation. The ability to test for mutations in different genes controlling behaviour is going to be important. (The extreme form of this will be to test for predisposition to schizophrenia).

2.5 Too broad a question to answer!

3. *Genetic disease*

3.1 Most genetic testing is in the research setting in the UK. There are pockets of well organised testing, e.g., for the thalassaemias. There will be an increasing call for this as more genes controlling disease phenotypes are uncovered. There is a role for the small start up company here.

3.2 None at all.

3.3 Information about ones genes and the mutations in them should be kept confidential. There is the possibility for too much abuse otherwise.

3.4 Too much to answer in one go here. Use cystic fibrosis as a test case and do the necessary logistical planning. There is already a lot of data here. The National Health Service has addressed some of these issues (speak to Martin Bobrow).

3.5 Yes, people with "poor" genes should be protected, particularly for insurance purposes. That is not to say they would not pay more for insurance, just not unreasonably more. One pays more if one smokes, why should one not pay more if one is *likely* to die young? They should not be prevented from getting insurance at all. The insurance companies will have to spread the risk anyway as they do already.

3.6 This will come as more genes are uncovered. CF again is a good example. If I were a carrier, I would want to know if my mate was one too.

4. *Economic benefits*

4.1 These are two separate questions. Once we understand the genes that are involved in controlling predisposition to disease we will be able to see which drugs work best for individuals with particular sets of genes. For example, some forms of hypertension and renal failure may be better treated by ACE inhibitors than others . . . depending on the genes involved.

Similarly, once the genes are understood the protein products may represent new points of intervention to treat the disease.

4.2 Somatic gene therapy does not represent a difference in principle (recombinant proteins and insulin are only one step from treatment with the gene). It is a difference in practice, though. Development costs are more uncertain. More important is efficacy at present.

4.3 No more so than in conventional drug discovery. The only problem is that the rules are not clear. No one knows who has strong patents and who does not. This is actually quite similar to the situation with recombinant proteins in the early 1980s.

4.4 Poor but improving. The implementation of the Clothier committee recommendations was very slow and poorly handled. Do not confuse the regulatory situation with access to venture capital. These are two different issues.

The UK is in a good position to carry out gene therapy because of the hospital infrastructure and research connections and the regulatory position. However, we really lost out at the start with there being no real initiatives. The USA has the lead by a long way. It is a pity that there is only one focused UK based gene therapy company (Therexsys).

4.5 These are the most likely products but there is great interest in animal breeding which will lead to more rapid ways to produce new strains of pigs and cattle.

5. *Research*

5.1 These are well rehearsed arguments. A complete map of the human genome will help us to locate important genes, including ones predisposing to diseases such as asthma and diabetes. The sequencing and mapping of all expressed sequences will provide very useful background information in this endeavour. A complete sequence of the genome will ultimately be useful, but I don't think there is any hurry for this goal (in contrast to the map).

5.2 A study of the different mutations in the human genome and comparisons within human populations will be very illuminating for the population geneticists. It may also be important for forensic purposes. i.e., telling the ethnicity of a person by sequencing a set of genes from a blood or tissue sample.

5.3 It is always a mixture of both.

5.4 Yes, of course, but transgenic technology (mice) is helping us to understand this. There may be the possibility of targeting genes to particular places in the genome where effects can be predicted.

5.5 No, but the Wellcome Trust have really helped in the UK.

6. *Evolution*

6.1 There is some—read Steve Jones book, "The Language of the Genes".

6.2 Steve Jones discusses this in the last chapter much better than I can. The short answer is, it will, but it is not clear how.

6.3 A similar answer to 6.2 given the above (5.3).

6.4 We will continue to pursue scientific knowledge. We want to know the relationship between genotype, phenotype and the environment. All human behaviour is based on this!

6.5 As this would be only the extremes, the answer is not much. However, any form of genocide must be subject to ethical, scientific and moral review. It will not happen in any large scale way anyway (except in war and this is not a scientific endeavour, nor is it controllable).

6.6 It is determined and not random. Therefore, it is very different.

6.7 Under certain controlled conditions the answer has to be yes, if safe and predictable technology allows. It is unlikely that these procedures will take the place of natural breeding and selection (. . . it is too much fun).

GENE THERAPY, GENOMICS COMPANIES AND DRUG DISCOVERY

There are two types of Genomics companies—those taking a predominantly sequence-based approach and those using genetics and positional cloning. These are not to be confused with the Gene Therapy companies who are using virus vectors or liposomes to deliver genes to particular cells or tissues.

The sequence-based genomics companies, like Human Genome Sciences, Incyte and Darwin are sequencing many thousands of cDNAs and by comparing the sequences to those in existing data bases, are identifying new members of existing gene families and many other new proteins. This information will be of use in drug discovery in many ways, but most importantly in being able to identify *all* members of particular protein families

(i.e., seven transmembrane receptors or proteases) which are historically good drug targets. Another good example of the use of this kind of information was the recent discovery of the DNA repair genes involved in hereditary non-polyposis colon cancer (HNPCC). Homology of the bacterial genes, Mut S and Mut L to MSH 2 and MLH 1 were very instructive in the subsequent identification of these two human genes.

The second type of Genomics company (illustrated by Sequana Therapeutics, Millennium and Myriad Genetics) is taking a more genetic approach. They are "positional cloning" companies. That is to say they are using the correlation of the inheritance of microsatellite markers (genetic maps) in the DNA of families with disease to the inheritance of the disease phenotype. A recent review in Science [Lander & Schork (1994). Science *265,* 2037-2048.] covers the sophisticated genetic approaches available for the analysis of complex traits in more detail.

The rationale of these companies is that uncovering the genes and the identification of the mutations in them that, in concert with the environment, cause disease will give new insights into the mechanism of the pathology of the disease. Further validation of this approach (if any is needed) comes from the exciting discovery of the location of several genes involved in predisposition to Type 1 diabetes. [See Davies, *et. al.* (1994). Nature *371,* 130–136., Hashimoto, *et. al.* (1994) Nature *371,* 161–164.] This sort of insight will not come directly from collecting sequences from "diseased" tissues or cell lines or by classical functional gene cloning. Nevertheless, these new target identification approaches are not mutually exclusive.

The key to all these sophisticated technologies is the ability to obtain and correlate information quickly and efficiently. The correlation of genetic data bases with three dimensional protein structure and metabolic function data bases will become possible through accessing the Internet via Mosaic and other devices. *No* company involved in modern drug discovery can afford to ignore the importance of obtaining biological data electronically and in real time. It is surprising that Bioinformatics is often the poor relation of the IT world in most large pharmaceutical companies. It will take some time before new drugs will emerge from the new targets identified by the use of genetics and genomics. Diagnosis of disease, however, will be helped quickly by the discovery of mutant predisposing genes. Several new and important genes and their mutations have been published in the last few weeks. In particular BRCA1 has been identified, a gene which predisposes to breast cancer [Miki *et. al.* (1994) Science *266,* 66–71, Futreal, *et. al.* (1994). Science *266,* 120–122.] and the role of p16 and mutations in it in melanoma has been clarified. [Hussussian *et. al.* (1994). Nature Genetics *8,* 15–21, Kamb *et. al.* (1994) Nature Genetics *8,* 22–26.] The genetic evidence suggests that several more cancer genes will be found by examining those proteins controlling the cell cycle.

The other important use of prognostic genetics is in sorting out the molecular basis of differential drug effects. Many drugs only work in a subset of people for whom they are prescribed. Polymorphisms in drug metabolizing enzymes (e.g., cytochrome P450s) are responsible for some of these differential effects. Identification of the mutations (polymorphisms) in drug targets correlating with drug response (e.g., the dopamine D4 receptor and dopamine antagonists) will be a very active field in the near future and increased target definition will be possible.

The concept of genetically validated targets is not new: several drugs—e.g., mevacor (an HMG CoA reductase inhibitor) and finasteride (a 5 α reductase inhibitor) owe their development to an understanding of human genetics. The association of ApoE4 with late onset Alzheimer's disease provides a new entry point into understanding the complex pathology of this neurodegeneration. The biochemical relationships between APP, ApoE4 and the yet to be discovered gene on chromosome 14 will almost certainly be the basis of searches for new drugs to combat the disease. The ApoE4 story also highlights the need for companies and project groups to be poised to utilise the genetic discovery to drive the research forward.

Often the function of the mutated gene will not be obvious from the amino acid sequence. Rapid ways to predict (and test) the function of unknown cloned genes are required. Yeast and other lower eukaryotic cells provide useful test systems but will not provide the complete answer. It is salutory to remember that over 50 per cent of all the genes sequenced in the yeast genome project (and over 50 per cent of the genome has now been sequenced) have no known or predictable function.

We are now entering a new era of drug discovery driven by advances in molecular genetics. The diagnose and treat paradigm will give way to predict and prevent. The current cost of health care in the USA and Europe is putting pressure on prices and profitability in the whole industry. The only way to succeed in this environment is to innovate: real innovation starts in the laboratory. Advances in molecular genetics and an understanding of how the human genome is put together is the most exciting and revealing work being done in all of biology today and will certainly lead to new drugs to combat common, poorly treated diseases.

Memorandum from D V Owen, Manager, The Diagnostics Club (HGC102) (January 1995)

I wish to submit comments on a personal basis concerning the screening of a population or the testing of an individual for a disease which has a genetic component (items 3.3, 3.4 and 3.6).

I have progressive Multiple Sclerosis, a disease which is thought to have a genetic component. It is a condition which causes increasing disability and pain over many years, and for which there is no treatment. Also I have a very healthy active teenage daughter.

While it is difficult to deal with one's own progressive disease I would find it impossible to handle the news that my daughter had a predisposition to a condition for which she could take no measures to prevent or reduce.

Regulation and legislation should do everything possible to prevent an individual being forced to find out (e.g., for insurance or employment) about a future disease for which there is no prevention or treatment.

Memorandum from The Human Genome Organisation (Europe) (HGC103) (23 January 1995)

You wrote to me on 8 November 1994, inviting HUGO Europe to submit evidence to the Committee. As I explained to you on the phone shortly afterwards, at the time of your request the Board of HUGO Europe comprised 14 members, eight from the UK and six from other European countries. As the majority of the UK members had already been invited to submit evidence to the Committee in an individual capacity, I was rather doubtful of being able to achieve a single response which was representative of the full Board. Nevertheless we agreed that it would be useful to try to achieve this. Consequently, all Board members were invited to submit responses to me, to be collated into a single representative submission.

In the event (and rather as I had anticipated) I received no replies from UK members, who felt that they could not add to their individual submissions. However, I did receive responses from Board members in three other countries and copies of these are enclosed with this letter. As discussed with your office today, I feel I am not armed with sufficient replies to attempt to produce a collective, "HUGO Europe" view on the questions posed, although (including the enclosed) the individual views of most of the Board members should have been submitted to you.

Letter from the Clerk of the Committee to HUGO Europe

1. Why is it worthwhile to map and sequence the human genome? What are the relative advantages of mapping expressed genes only versus completely sequencing the genome?

2. What will it tell us about the human species and the individual that would not otherwise accrue from piecemeal studies?

3. To what extent are human characteristics determined by the genome and to what extent does the environment influence the expression of genes?

4. How much is understood about the organisation of coding information in the genome? Is it conceivable that interventions such as those produced by gene therapy might have unforeseen effects?

5. How is the Human Genome Project project organised; when will it have reached a conclusion?

6. What is the current position of the research? How many loci have been mapped? How many genes have been mapped? What is the resolution of the genetic map? What is aimed for in the future? Why were these targets chosen? What are the comparative advantages of sequencing genes and intergenic DNA?

7. What have been the past costs: what are the future costs likely to be?

8. Could the information have been acquired more cheaply in another way?

9. What has the UK's contribution been absolutely and relative to other countries involved? Is it increasing or diminishing? Why?

10. How does the HGP stimulate and benefit from comparable studies of other organisms of basic scientific, pharmaceutical and/or agricultural importance?

Submissions

ANSWERS TO THE QUESTIONS POSED IN THE COMMITTEE'S LETTER TO HUGO EUROPE OF 8 NOVEMBER 1994.

From: Professor Ulf Pettersson, Head, Department of Medical Genetics, University of Uppsala, Sweden

1. The sequence of the human genome will provide a catalogue of information which will benefit all biomedical research in the future. The advantage of sequencing the whole genome is that we will then know

that we have all the information available. However, a quicker way to acquire the most relevant information is of course to study the expressed genes. It is my opinion that both efforts should run in parallel.

2. The advantage of sequencing the whole genome rather than sequencing bits and pieces is that the process can be speeded up and methods developed which will provide the scientists with relevant information much quicker.

3. It will differ for different phenotypic characteristics. It appears, however, that the genetic component increases in significance as we learn more about our genes.

4. We lack information about the larger scale organisation of the genome. However, I do not suspect that this will lead to unforeseen effects, for instance in gene therapy.

5. This information is available in various descriptions of the human genome project.

6. Also, this question is answered by numerous publications in the field. As to the sequencing of genes and intergenic DNA, it is of course likely that more relevant information will be obtained from sequences of the genes. However, the intergenic DNA sequences are of importance to understand gene regulation.

7. I am not the best person to answer this question.

8. The strategies for the project have changed along the way. If we were to start again from the beginning with the knowledge that we have today, there are more efficient and cheaper ways to approach the sequence of the complete human genome.

9. This question should be answered by UK colleagues.

10. *No answer supplied.*

ANSWERS TO THE QUESTIONS POSED IN THE COMMITTEE'S LETTER TO HUGO EUROPE OF 8 NOVEMBER 1994

From: Professor Gert-Jan van Ommen, Head, Department of Human Genetics, University of Leiden, Netherlands

1. *Why at all?*

It will uncover a vast range of biological functions not otherwise traceable.

Genes versus whole genome

Pro: More focused for gene function

Contra: Chromosome/genome organisation (which plays a big role in gene expression and/or defects thereof) will not be uncovered.

2. *HGP versus piecemeal studies*

The latter are usually goal-directed and will continue to revolve around existing problems. So far, the genome project is uncovering 60 to 70 per cent new functions not found by piecemeal studies. In addition, the detection of disease genes has been boosted by an order of magnitude through the development of genome technologies.

3. *Genome versus environment*

Both are important. Due to its uncontrollable nature, the effect of the environment will only be decipherable when the genetic contributions are more universally understood.

4. *Organisation of coding information; unforeseen effects of gene therapy*

The organisation of coding information is fairly well understood but (see 1) the genome project may and will unravel organisational levels that are presently unforeseen. As with all therapies, gene therapy will have almost certainly have unforeseen effects. This is why it needs to be restricted to the patient's own lifetime. Hence only somatic gene therapy should be developed as the balance between the effects of the patient's disease and the potential side effects of the therapy can be properly evaluated.

5. *Organisation and milestones of the genome project*

Three stages: 1989–94 Genetic and Physical Map—1995–99 Gene Map and Structural Analysis—2000–2004 Full Scale Sequence Analysis

6. *Current status, future aims*

See *Science,* October 1994, for status.

Future aims are full genetic, physical and sequence maps. The genetic maps need to be refined to 100 kb resolution for linkage disequilibrium studies essential for multifactorial disease.

7. *Past costs; future costs*

? (I do not have all these details)

8. *Other ways to acquire these insights*

Two answers: (i) There is no other way; (ii) One may mistakenly think that it is more economical on public funds to let the private sector have a go at it. The cost in the future will be much higher then, firstly through the monopolies arising from patents, secondly through the delay in development of applications due to non-competition and exclusivity.

9. *Contribution of UK, absolute/relative*

Absolute—?

Relative—substantial, relative to the expenditure, due to the good status of medical genetics in the UK. Including financial sources such as the MRC and the Wellcome Trust, and developments in the UK such as the Sanger Centre, the UK's HGMP Resource Centre, the European Bioinformatics Institute, etc., the contribution will increase in the foreseeable future rather than decrease.

10. *Stimulation/interaction HGP and studies of other organisms and disciplines*

(i) The HGP has a great stimulating effect on cell biology and, in turn, derives much from it, especially from animal comparative genetic studies in the field of transgenic and knock-out mouse pathophysiology and natural animal genetic (disease) studies.

(ii) The studies in the pharmaceutical field will benefit enormously from the increased biological insights. It would be wise to consider the basic currency, the gene sequences, as freely available seed capital rather than as intellectual property.

ANSWERS TO THE QUESTIONS POSED IN THE COMMITTEE'S LETTER TO HUGO EUROPE OF 8 NOVEMBER 1994

From: Professor Harald zur Hausen, Director, Deutsches Krebsforschungszentrum (DKFZ, the German Cancer Centre), Heidelberg, Germany

1. The human genome contains basically all the information that is necessary to build and run a human body. Thus, for a real understanding of the functioning, and hence any occurring malfunctioning, knowledge of this basic information is a pre-requisite. There will be a huge improvement in health care resulting from this research, with medical treatment becoming much more efficient and cheaper, even for diseases which are already curable today. The starting point will be better detection and prevention methods. The higher standard of health of the population and the lower cost of health care will make the Human Genome Project (HGP) financially very worth while, without beginning to take the social aspects into account. In comparison with the annual budget spent on health care in the Western world alone, the costs for the unravelling of the human genome sequence are minute, even at today's price. In addition, there will be a huge spin-off in new technologies resulting from this research with tremendous implications, for example, on the environment.

Sequencing genes only will quickly provide the most obvious of the information contained in the genome, enabling identification of genic mutations and hence the development of relevant test systems, for instance. However, most information on gene regulation lies outside the coding sequences. Thus, the understanding of gene function also requires knowledge of intergenic sequences, particularly since many aspects of regulation and interaction, such as DNA conformation, are yet known only partially or (most probably) not at all. Also, many implications genomic organisation and performance cannot be predicted without having the basic sequence information.

2. Small "piecemeal" studies will never allow understanding of the large number of correlations between various parts of the genome and will prevent insight into the molecular operation of the human body other than for very limited areas.

3. There is only a chance of answering this question reasonably, even in a partial way, after the information from the HGP is available.

4. For specific groups of genes the organisation of the coding information is very well understood. This does not mean, however, that there are no other means of regulation and organisation unknown today. On the contrary, I would expect that such mechanisms would be found during the HGP.

Gene therapy on a well defined aspect of the genomic information is extremely unlikely to produce any unforeseen effects. Undefined "shotgun" interventions should be avoided, however, until the information necessary for an accurate definition of the molecular sequences is acquired.

5. The HGP is not organised centrally but has developed gradually, and mainly on national lines, as a result of the (rather nationally oriented) funding situation. However, there is an ever increasing number of international links between research groups, frequently based on the traditionally good personal contacts between laboratories, since there is world-wide acceptance that only a world-wide correlated effect (and the ideas of many people) will suffice in tackling the immense task of the HGP.

The conclusion of the HGP is difficult to define since it includes much more than the mere deciphering of the sequence information. Still, one definition could be the complete sequencing (as far as necessary) of one genome each of: man; mouse; the worm *Caenorhabditis elegans*; the fly *Drosophila melanogaster*; the yeasts *Saccharomyces cerevidiae* and *Schizosaccharomyces pombe*; and the bacteria *Escherichia coli* and *Bacillus subtilis.*

6. The human genetic map has a resolution of about 3cM which is very roughly equivalent to 3 Mbp. However, there are huge variations between different areas and chromosomes. For physical markers (STSs), one per about 100 kbp is the aim for the end of 1995, a density thought to be sufficient for the physical mapping of the genome.

7. This question is difficult, if not impossible, to answer since the definition of the HGP is vague. What aspects of the work should be included? For example, is the large amount of genetic data accumulated on the fruit fly Drosophila for more than a century a part of the HGP (which I think it partially is)?

8. No!

9. The contribution of the UK has been substantial due to the traditional strength in this scientific field. Compared to other countries, the contribution ranges second behind the USA and in front of France, which is the closest "competitor" for second place. The British share is diminishing apart from some specially funded aspects, such as the large scale sequencing at the Sanger Centre, Cambridge, due to an overall worsening in the (state) funding situation.

10. *No answer supplied.*

Letter to the Clerk of the Committee from the Biotechnology and Biological Sciences Research Council (HGC104) (23 January 1995)

I am responding on behalf of Professor Blundell to your letter of 25 November 1994. As you are no doubt aware, the study of human genetics does not fall within the remit of the BBSRC but lies within the ambit of the Medical Research Council and a number of medical research charities. We have not therefore attempted to answer any questions in the list attached to your letter. On the two specific questions you pose we would respond as follows:

1. *What effect has the reorganisation of the Research Councils had on the proportion of genetics based research sponsored by the BBSRC (or its previous bodies)?*

The aggregation of former AFRC and SERC genetics based research has, concentrated a significant proportion of genetics based research in the UK under the aegis of BBSRC but the total volume of genetics based research is at present relatively unchanged. However, in the future, because BBSRC's remit has been broadened to underpin all the biologically based industries and health care, the Council expects to receive a greater number of applications for support from scientists who might previously have sought funding elsewhere. In addition, work on human disease will be reinforced through animal models developed through BBSRC funding in its institutes and in the universities and transgenic animal technology has already been transferred to the pharmaceutical industry for the production of biopharmaceuticals in milk.

2. *To what extent has genetic research sponsored by the BBSRC benefited from the Human Genome Mapping Project?*

The BBSRC currently supports an initiative in Plant and Animal Genome Analysis and, in doing so, liaises closely with the Human Genome Mapping Programme and the MRC Human Genome Resource Centre. The

BBSRC programme has benefited from access to molecular tools such as cDNA libraries, YAC technology, sequencing robots, etc. Collaboration with the Human Genome Resource Centre has allowed important access to databases for use in comparative mapping, enabling animal mappers to acquire information about the position of candidate genes on the human genome. In future these benefits may be reciprocal allowing human geneticists access to information about the genetic bases for complex diseases, such as osteoporosis for which there is a model in the chicken. There is also close liaison between BBRSC and MRC on the development of appropriate informatics to underpin genome research.

Memorandum from Dr S Minter, Tepnel Life Sciences PLC (HGC105) (24 January 1995)

It is rare for small companies associated with diagnostic testing to have the opportunity to express their views. I very much welcome this and would like my views considered in the evaluation being made by the Science and Technology Committee of the House of Commons. These opinions expressed are my own personal views and will mainly be restricted to the questions outlined in the notice published in the Diagnostics Club "Exchange" publication. Our company is a member of the Diagnostics Club.

In detail my views are as follows:

3. *Genetic Disease*

3.1 By definition if a disease is being diagnosed as genetic disease, then it is being diagnosed as such. The question should be: "If more information were known about the genetics, and specifically the sequences of the genes within man, would more diseases be recognised as genetic?" The answer would obviously be yes. With this information diagnoses could be made earlier and more accurately.

3.3 Information about the gene type of an individual should be treated as all other medical information, i.e., confidential to the patient.

3.4 Genetic testing should be made available to all mothers to be, or all ages. Genetic testing should also be made available to families with a predisposition to genetic disease. The regulation of this testing is already in place but obviously needs to be expanded in terms of availability. The costs of such testing should be borne by individuals in the private sector, or by the NHS if this is extended into screening.

3.5 The information must remain confidential to the patient.

3.6 If they have a predisposition, or are more likely to be affected, then the opportunity for such screening should be made available to both parents and potential offspring.

4. Economic Benefits

4.1 Treatment can be matched to diagnosis. Long-term benefits would accrue from the structural information that it is possible to obtain from a gene sequence. This could aid targeted drug design.

4.2 The practical problems of "drug" stability and transport into a developing cell are currently enormous.

4.3 The ability to patent sequences has, and will slow down and in some instances, stop the commercial applications of the research findings. Only the large companies (not necessarily the most innovative) will have access to these sequences.

5. *Research*

5.1 To completely understand the genome, it is essential to know the sequence. Mapping expressed genes, i.e., cDNA, is quicker and cheaper. By doing so, it is probable that information concerning the control of these genes will be lost. It is therefore essential to sequence all of the genome.

5.2 Unknown.

5.3 Both play a role.

5.4 Yes.

5.5 More could be done.

Memorandum from The Scottish Office, Home and Health Department (HGC107) (25 January 1995)

1. This memorandum provides a Scottish perspective to the following questions which were posed to the Department of Health.

1.1 Which genetic diseases are being diagnosed and what are their frequencies in the UK? What proportion of diseases stem from a single genetic defect? How many of these are currently diagnosed? What is the incidence in the UK population of known carriers and sufferers of each related disease and disability? How does this incidence in the UK vary from that in the world generally and how does it vary between groups in the UK?

1.2 How is routine diagnosis currently organised? How is it likely to be organised in the future?

1.3 How much is currently being spent on developments arising from human genetics research? How much has been spent in the past? How much is projected to be spent in the future? How does the research effort into particular genetic diseases correlate their frequency?

Genetic diseases

2. There are no significant differences in the pattern of genetic disease in Scotland compared to the rest of the UK other than those due to a lower incidence of ethnic minority communities. The information provided to the Committee by the Department of Health as to the frequency of individual genetic conditions, covers the UK and is representative of the position in Scotland.

Diagnostic and clinical services

3. The population of Scotland is served by a comprehensive and integrated clinical and laboratory genetic service. This is provided by four regional genetic centres in Edinburgh, Glasgow, Dundee and Aberdeen together with the Scottish Molecular Genetics Consortium. Each centre provides the clinical genetic diagnostic and counselling service and associated laboratory support, for the population of its area. The Scottish Molecular Genetics Consortium provides a comprehensive service of DNA analysis for the diagnosis and prevention of genetic disease in Scotland.

4. The service aims to provide for the following vital elements:

— the ascertainment of families/individuals with an inherited predisposition to a genetic condition;

— the provision of adequate DNA diagnostic services;

— appropriate genetic counselling;

— adequate clinical management and screening or follow-up for those individuals identified to be at high risk.

Genetics research

5. The main responsibility for Government funded research into human genetics lies with the Medical Research Council (MRC) and the Scottish Office Home and Health Department does not now expect to fund genetics research directly. Prior to recognition of the lead position of the MRC, the Department had funded genetics projects in the period since 1990, to the value of £1.4 million. The Department maintains close contact with MRC in this area and contributes to the peer review of proposals for research by participation in the relevant Boards and Committees, contributing particularly in the assessment of health service relevance and value. The Department participated in the recent review by MRC of their Human Genetics Unit which is based in Edinburgh.

General

6. The Department recognises that particular ethical sensitivities arise in relation to human genetics. Changes in the definitions, parameters and regulatory oversight of the ethical dimension of human genetics activity,

demonstrate clearly the rapidity with which such mechanisms could become marginalised by the advance of the knowledge base and available technology. We recognise the value of the role of the Director General of the Research Councils is undertaking in developing operational criteria and practice guidance which is common to all Research Councils and which will address and keep under review the important ethical considerations in this research area. The MRC have published useful guidance on the ethics of research in several areas and the Health Departments have had the opportunity to input to these.

Letter from Mrs M Ferguson-Smith (HGC108) (18 January 1995)

My experience in Human Genetics is mainly in Clinical Laboratory Genetics and in the development and the provision of diagnostic services over a 30 year period. Before my early retirement from the new NHS, I was greatly privileged to have an opportunity to play a part in this most important field of clinical development. My main area of work and research involved all aspects of prenatal diagnosis, screening and fetal loss as well as teaching of other professionals, training of scientists and communication with relevant groups in the community.

My experience has taught me that those working in this field often forget that the general public's concept of the subject can differ greatly from that of the professionals. The general problem of misunderstanding is also compounded by other basic factors, for instance:

1. *Failure for those taking part in discussions to clearly define the terms;*

Most frequently confused terms are the definition of *screening tests* = the assessment of *risks* for a specific condition in a selected population; *diagnostic test* = positive or negative *diagnosis* for a specific condition in an individual;

Genetic testing = *diagnostic tests* determining a genetic status of an individual or a population using DNA technology.

Genetic counselling = genetically and clinically informative consultation, referred to by clinical geneticist or support staff as "counselling" and often confused with therapeutic or pastoral counselling which is supportive, non genetic and can be long term.

Ethics, morality and legality often not clearly defined as separate but interacting issues.

2. *Differences in attitude.*

Failure for those involved in research and those involved in provision of the service to recognise the differences of approach to patient material.

There is a fundamental difference in the concept of *what* is the status of the patient. (For one the patient is the means to an end for the other the end in itself)

3. *Generalisations*

There is at times, a tendency by those opposed to genetic research to use general statements which have an universal appeal but which in real terms have very little practical implications. (Failure to substantiate a case with data). These statements evoke emotions, take up time and lead to confused conclusions.

4. *The difference in the principles of Human Genetics and the concept of Eugenics.*

These two are often confused. This is understandable, since within our memory scientists and doctors become servants to a political ideology. This memory evokes an extreme and sometimes violent desire to protect the dignity of a human life, but it should not be confused with the desire and the responsibility of the scientists to improve the quality of life. It is therefore necessary for the Government to impose ethical rules to protect the community and the individual, as well as the individual's right to knowledge and the freedom to choose.

General Comment:

I note that the inquiry makes no reference to the education or training within the community or the profession.

My particular concern is the training within the Clinical Diagnostic Services. Apart for the clinicians, the diagnostic laboratory services are staffed by scientists without whose expertise the speciality would have no

tangible meaning. These individuals, after obtaining a higher degree, need a minimum basic training of two to three years on the job. Despite automation most interpretations of results in clinical laboratory genetics are based on individual skills and knowledge. So far the Government NHS reforms have failed to recognise the training of staff as part of a good quality and responsible NHS service. Mistakes in interpretation of results can have very costly and serious implications both in destruction or in the quality of a new life and in the long term are less cost effective than money spent on training.

I am very much aware of the tremendous importance and responsibility placed on this inquiry. Its conclusions will effect the future polices on human genetic research and consequently the quality of services provided to the community and for the individual. I wish the committee well!

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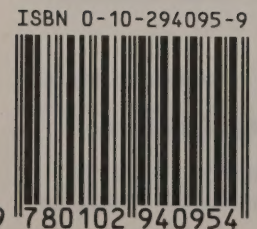

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